“A STUDY ON THE ANAESTHETIC AND ANALGESIC EFFECTS OF INTRAVENOUS DEXMEDETOMIDINE AS PREMEDICATION FOR SPINAL ANESTHESIA”

DISSERTATION

SUBMITTED TO

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF

M.D ANAESTHESIOLOGY

BRANCH X

APRIL 2016

CERTIFICATE

This is to certify that this dissertation entitled **"A study on the anaesthetic and analgesic effects of intravenous dexmedetomidine as premedication for spinal anaesthesia"** is a bonafide record of the work done by **Dr. Suzanne Prasad** under guidance and supervision in the Department of Anaesthesiology during the period of her postgraduate study for **M.D Anaesthesiology [Branch-X]** from 2013-2016.

Dr. V.G. Jayaprakash, MD
[Guide]
Professor
Department of Anaesthesiology
Sree Mookambika Institute of Medical Sciences
Kulasekharam, Kanyakumari District:
Tamil Nadu 629161
Ph: +919447833999

Dr. Rommy Geever T, MD
[Co-guide]
Assistant Professor
Department of Anaesthesiology
Sree Mookambika Institute of Medical Sciences
Kulasekharam, Kanyakumari District:
Tamil Nadu 629161
Ph: +918940096867

Dr. Rema. V. Nair
M.D., D.G.O.,
Director
Sree Mookambika Institute of Medical Sciences
Kulasekharam, Kanyakumari District
Tamil Nadu 629161

DECLARATION

In the following pages is presented a consolidated report of the study **"A study on the anaesthetic and analgesic effects of intravenous dexmedetomidine as premedication for spinal anaesthesia"** a quasi interventional trial, on cases studied and followed up by me at Sree Mookambika Institute of Medical Sciences, Kulasekharam from 2014-2015. This thesis is submitted to the Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of MD Degree examination in Anaesthesiology.

Dr. Suzanne Prasad
Junior Resident
Department of Anaesthesiology,
Sree Mookambika Institute of Medical Sciences,
Kulasekharam, Kanyakumari District.
Tamil Nadu 629161.

"A STUDY ON THE ANAESTHETIC AND ANALGESIC EFFECTS OF INTRAVENOUS DEXMEDETOMIDINE AS PREMEDICATION FOR SPINAL ANESTHESIA"

Dissertation

Submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

In partial fulfillment of the requirements for the award of the degree of

M.D ANAESTHESIOLOGY

Branch X

April 2016

ACKNOWLEDGEMENT

I thank God almighty, for all his blessings without which this work would not have been possible.

I express my heartfelt gratitude to our Director Dr. Rema V. Nair and our Chairman Dr. Velayudhan Nair for providing me the infrastructure and for permitting me to carry out the study in this institution. They are the founders and pillars of the various activities initiated in our institution.

I thank my HOD Dr. A Thavamani, for the creative suggestions, timely advice and constant encouragement. It has been a tremendous and wonderful experience to work under his guidance.

I thank my guide Dr V.G. Jayaprakash for his valuable help, suggestions and supervision throughout the study. He lent his full support in times of difficulties that I encountered during this study period without which this dissertation would not have been completed on time. His encouragement from the inception of this research to its culmination has been profound.

I humbly thank Dr. Rommy Geever T and Dr. Mahilamani whose support, guidance, help, critical views and comments kept me in full swing throughout my study period. Their suggestions were very valuable at each stage of my dissertation work. I am indebted to them for their guidance and support throughout my post graduate days.

I am grateful to Dr. Subramaniam for his valuable support and constant encouragement.

I thank Dr. Gopalakrishnan, Dr. Anand, Dr. G Parvathy for their guidance during my initial study period.

I also extend my sincere thanks to Dr. Prashanthan, Dr. Saji, Dr. Beula, Dr. Ravishankar and all the staff members of Anaesthesiology for their support.

I thank Dr. Jisha Roy Babu, my co-pg, for her valuable and timely help to complete my study on time. I am grateful to my senior post graduates Dr. Rakhi S.P and Dr. Mohsina Basheer and my junior post graduates Dr. Sahil, Dr. Archana, Dr. Sathish and Dr. Anitha for the various technical aspects of my study.

I am grateful to my family members for relieving me of my social responsibilities so that I could fully focus my attention on this study.

Without the whole hearted cooperation of my patients, this thesis would not have reached a conclusion. I express my sincere gratitude to all my patients at Sree Mookambika Institute of Medical Sciences, Kulasekharam.

Dr. Suzanne Prasad

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVATIONS USED

α	-	Alpha
β	-	Beta
µg / mcg	-	Microgram
AR	-	Adrenergic Receptor
ASA	-	American Society of Anaesthesiologists
BP	-	Blood Pressure
bpm	-	beats per minute
CNS	-	Central Nervous System
CO	-	Cardiac Output
CO_2	-	Carbon Dioxide
CSF	-	Cerebrospinal Fluid
CVS	-	Cardiovascular System
DBP	-	Diastolic Blood Pressure
dL	-	Decilitre
$ETCO_2$	-	End-tidal Carbon Dioxide
G	-	Gauge
HR	-	Heart Rate
hr	-	Hour
ICU	-	Intensive Care Unit
IM	-	Intramuscular

Inj.	-	Injection
IV	-	Intravenous
Kg	-	Kilograms
L	-	Litres
m	-	Metre
MAP	-	Mean Arterial Pressure
Meq/L	-	Milliequivalents/Litre
mg	-	Milligrams
min	-	Minute
mL	-	Millilitres
mmHg	-	Millimetres of Mercury
O_2	-	Oxygen
^oC	-	Degree Centigrade
PR	-	Pulse Rate
RR	-	Respiratory Rate
SAB	-	Subarachnoid Block
SBP	-	Systolic Blood Pressure
sd	-	Standard Deviation
sec	-	Seconds
TURP	-	Transurethral resection of prostate
VAS	-	Visual Analogue Scale

ABSTRACT

TITLE OF THE STUDY:

"A study on the anaesthetic and analgesic effects of Intravenous Dexmedetomidine as premedication for Spinal anaesthesia''.

BACKGROUND AND OBJECTIVES:

Spinal anaesthesia is a widely practiced anaesthetic technique for lower abdominal and lower limb surgeries. Dexmedetomidine is a highly selective α2 - adrenergic receptor agonist with a relatively high α2/α1 activity. The present study evaluates the use of intravenous dexmedetomidine as premedication in bupivacaine induced spinal anaesthesia.

METHODS:

After approval of institutional ethical committee, a total of 60 patients of ASA 1and 2 were enrolled in this study with written informed consent. Half the patients received i.v Dexmedetomidine 0.5μg/kg bolus over 10 minutes and the remaining half received same volume of normal saline similarly. Heart rate, systolic and diastolic blood pressures were recorded periodically; onset, level and duration of sensory and motor blockade assessed, and sedation score and time request for rescue analgesia were also noted.

STATISTICAL ANALYSIS:

The data was analysed by SPSS 16.0 with independent t-test.

RESULTS:

In this quasi interventional study both the groups were comparable considering age, sex, height and weight. No significant biphasic change in heart rate, mean arterial pressure or cardiovascular variability was observed after administering Dexmedetomidine. The requirement of Inj. Atropine and Ephedrine were comparable in both the groups. The time for two dermatome regression of sensory blockade, the duration of motor blockade and the time of request for post-operative analgesia were significantly prolonged in the study group. Furthermore, the sedation scores were relatively higher in the study group.

IMPRESSION:

This study proves that i.v Dexmedetomidine as premedication enhances the duration of sensory and motor blockade in Bupivacaine-spinal anaesthesia with stable hemodynamic parameters, improved analgesia and better sedation without ventilatory compromise.

Key words: Dexmedetomidine, spinal anaesthesia, bupivacaine.

INTRODUCTION

Spinal anaesthesia also called subarachnoid/intrathecal block is a popular technique carried out for a variety of infraumbilical operative procedures. The advantages are faster onset with effective sensory and motor blockade which has been well established and widely accepted.

In this technique, to manipulate the spread of the local anaesthetic via the cerebrospinal fluid so as to provide an adequate block that ensures acceptable plane for the proposed procedure without needless extensive spread is a challenge to any anaesthesiologists[1].

Spread of the anaesthetic to higher levels may result in complications like paralysis of the intercostal muscles and the diaphragm causing respiratory crisis and may also affect the cardio-accelerator fibers which in turn affect the ability to control heart rate which can end up in cardio-respiratory arrest and death in extreme cases if timely management is not provided.

The surgical blood loss and other perioperative complications under spinal anaesthesia are less compared with general anaesthesia. The risks of general anaesthesia includes problems with airway management - difficult intubation in patients with anatomical abnormalities and possible need for postoperative ventilation for smokers or patients with irritable airway which can produce undesirable side effects in borderline hypertensives and geriatric patients.

Bupivacaine, an amide local anaesthetic, is the most commonly used drug for spinal anaesthesia. Over time different agents is being tried as adjuncts for delaying the span of spinal analgesia like epinephrine, phenylephrine, adenosine, magnesium sulphate, clonidine etc. the possible advantages of using these adjuncts include reduced local anaesthetic dose requirements which helps avoid the adverse effects of local anaesthetics, delayed onset of perioperative pain, reduced analgesic requirements, and better operating conditions for the surgeon.

Dexmedetomidine is an eminent, potent α_2-adrenoceptor agonist with 1000:1 α_2/α_1selectivity and a half-life of 2-3hrs[2]. It decreases the local anaesthetic dose requirement, provides anxiolysis, sedation and sympatholytic activity, and improves perioperative hemodynamics by attenuating blood pressure and heart rate. The faster recovery of Dexmedetomidine has made its emergence as a sole agent for procedural sedation and for ICU sedation. The Federal Drug Administration (FDA) has approved the use of Dexmedetomidine as a sedative-analgesic in patients - adult and pediatric age group, undergoing minimal invasive procedures, with or without the need for tracheal intubation. The current clinical indications of Dexmedetomidine include:

- sedation for mechanically ventilated patients in ICU (for up to 24hrs as continuous infusion)
- Procedural or perioperative sedation of non-intubated.

Studies have shown a shorter onset of blockade and significantly

longer duration with intrathecal Dexmedetomidine as an adjunct with bupivacaine for regional anaesthesia with stable hemodynamic profile[3]. Only few studies have been conducted to study the effects of intravenous Dexmedetomidine during spinal anaesthesia. The present study assess the effects of intravenous Dexmedetomidine on patients posted for surgeries under spinal anaesthesia.

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE

The objective of our present study is to evaluate the effects of intravenous Dexmedetomidine as premedication on the onset, level and duration of sensory and motor blockade, analgesia and sedation in patients posted for infraumbilical surgeries under Bupivacaine (hyperbaric, 0.5%, 3mL) spinal anaesthesia.

SECONDARY OBJECTIVES

- The level of sedation achieved in comparison with control group.
- To evaluate the post-operative analgesia requirements relative to control group.
- To evaluate perioperative hemodynamic stability in the study group.
- To assess possible complications.

HYPOTHESIS AND SCIENTIFIC JUSTIFICATION

HYPOTHESIS:

Intravenous Dexmedetomidine as premedication for Bupivacaine spinal anaesthesia extended the span of sensory and motor blockade and the time of request for first rescue analgesia. It also provided arousable sedation without respiratory depression and maintained a stable hemodynamic profile throughout the perioperative period.

SCIENTIFIC JUSTIFICATION OF THE STUDY:

Neuraxial block for lower abdominal surgeries are becoming widely popular owing to its many advantages over general anaesthesia. Spinal anaesthesia consists of transient interruption of nerve transmission by injecting a local anaesthetic (Bupivacaine 15mg) solution in the subarachnoid space. The role of an anaesthesiologist is to render pain free surgical procedures.

Anxiety is the most prevalent presentation in patients in the perioperative period starting from few days prior to surgery and reaches its peak just before induction of anaesthesia. Anxiety is also an intraoperative problem in patients undergoing surgical procedures under regional anaesthesia which may be the reason for various manifestations like increase in oxygen consumption, respiratory rate and heart rate due to circulating

level of intrinsic catecholamines and their untoward effects. Control of anxiety and pain is a challenge to any anaesthesiologists in an attempt to control the metabolic derangements and for the safety and comfort of the patient.

Dexmedetomidine is an eminent, potent α_2-adrenoceptor agonist that acts centrally. It has the ability to sedate, hypnotize and provide analgesia, thereby extending the duration of sensory and motor block acquired with intrathecal block while still preserving patient arousability and ventilatory function. It can be used as premedication, during induction of anaesthesia intravenously and as an adjuvant for intrathecal block with Bupivacaine.

This dissertation is a study on the effects of i.v Dexmedetomidine 0.5mcg/kg as premedication for analgesia, sedation and prolongation of spinal anaesthesia in patients posted for surgeries under subarachnoid block with hyperbaric Bupivacaine 0.5% (3ml or 15mg).

REVIEW OF LITERATURE

Studies have been carried out earlier to study the action of intravenous Dexmedetomidine on Bupivacaine spinal anaesthesia. Kaya FN et al[4] conducted a double blind randomized placebo controlled trial study in 2010, on the effects of intravenous Dexmedetomidine comparing it with intravenous midazolam on spinal anaesthesia, analgesia and sedation in patients posted for TURP on 75 patients belonging to American Society of Anaesthesiologists' (ASA) 1 and 2 (n=25 in each group). Patients were given Dexmedetomidine 0.5 μg/kg, midazolam 0.05μg/kg or normal saline intravenously before intrathecal block with 15mg of 0.5% bupivacaine. Level of sensory block was relatively higher with Dexmedetomidine group (T4.6±0.6) than with midazolam group (T6.4±0.9; P<0.001) or saline group (T6.4±0.8; P<0.001). Time for sensory two dermatome regression was 145± 26 min in the Dexmedetomidine group which lasted longer (p<0.001) than the midazolam group (106±39 min) or the saline group (97±27). Span of motor block was alike in all the three groups. Dexmedetomidine seemed to delay the first time request for rescue analgesia (p<0.01) compared to midazolam and saline group, and reduced the analgesic requirements (p<0.05). The Ramsay sedation score was higher in the Dexmedetomidine and midazolam group of patients than in the saline group (p<0.001). It was concluded that, intravenous Dexmedetomidine prolonged spinal bupivacaine

sensory blockade, but not midazolam, and it also provided arousable sedation and added analgesia.

In the following sections basics of spinal anaesthesia, physiology and pharmacology of α_2-adrenergic receptors and their agonists are briefed.

SPINAL ANESTHESIA

Also referred to as 'subarachnoid block' (SAB), or 'intrathecal analgesia'. Spinal anaesthesia is produced when a local anaesthetic is injected into the subarachnoid space.

History

The first spinal analgesia was administered in 1885 by a neurologist James Leonard Corning when he accidentally pierced the dura mater while he was experimenting cocaine on the spinal nerves of a dog[5,6]. The first planned spinal anaesthesia was administered by August Karl G Bier on 16th August 1898 in Germany[7] with the help of his assistant Hildebrandt, he administered 3ml of 0.5% (15mg) cocaine in a man. Bier and his assistant even tried spinal anaesthesia by injecting cocaine into each other's theca[8], and after a few further experimentation recommended it for surgeries of legs, but had to give it up due to cocaine toxicity.

Anatomy

Anatomy of vertebral column and of the lumbar vertebrae in particular is crucial for every anaesthesiologists.

Vertebral column:[9]

The vertebral column is comprised of 33 vertebrae which protects the spinal cord. They include:

- 7 Cervical.
- 12 Thoracic.
- 5 Lumbar.
- 5 Sacrum (fused).
- 4 Coccyx (fused).[9]

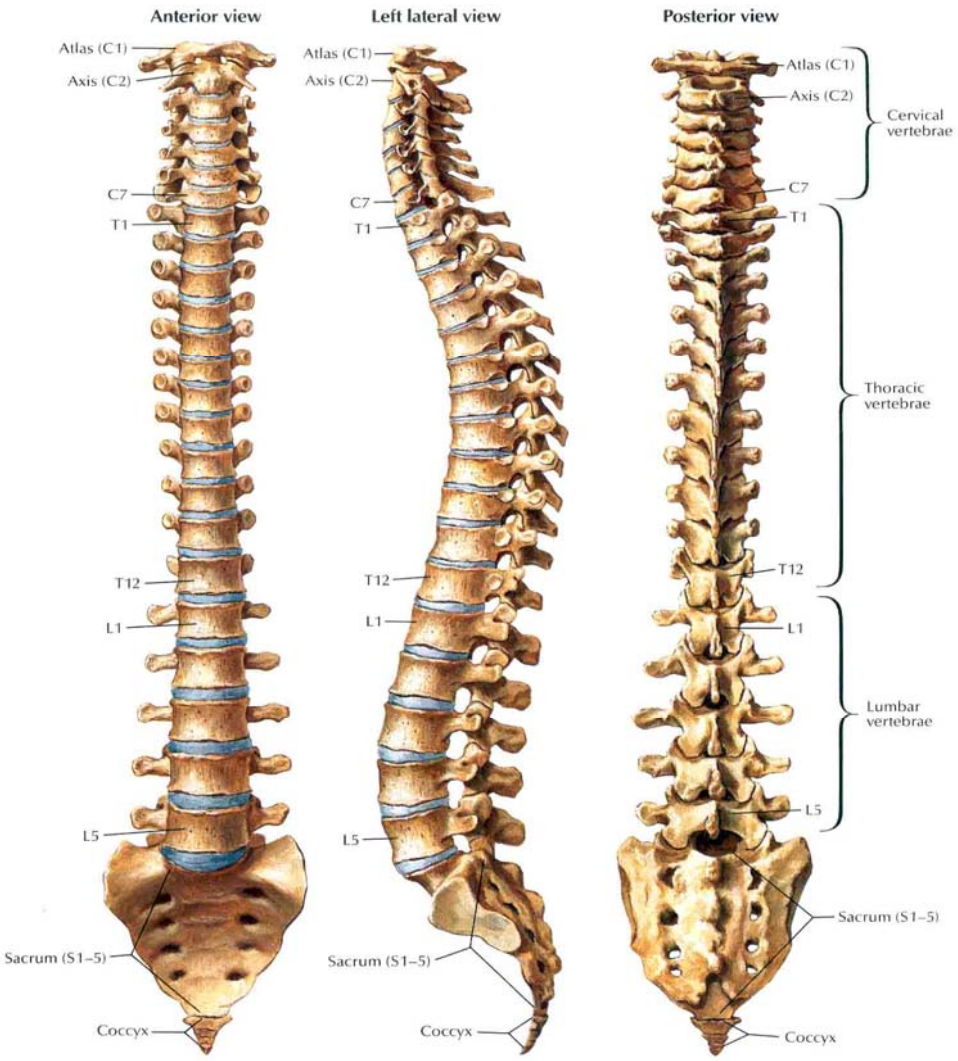


Figure 1. Vertebral Column

In adults, vertebral column has four curves which have a significant effect on spread on the drugs administered intrathecally:[9]

- Cervical and lumbar anterior Convexity curve
- Thoracic and sacral anterior Concave curve[9]

Vertebral ligaments[9]

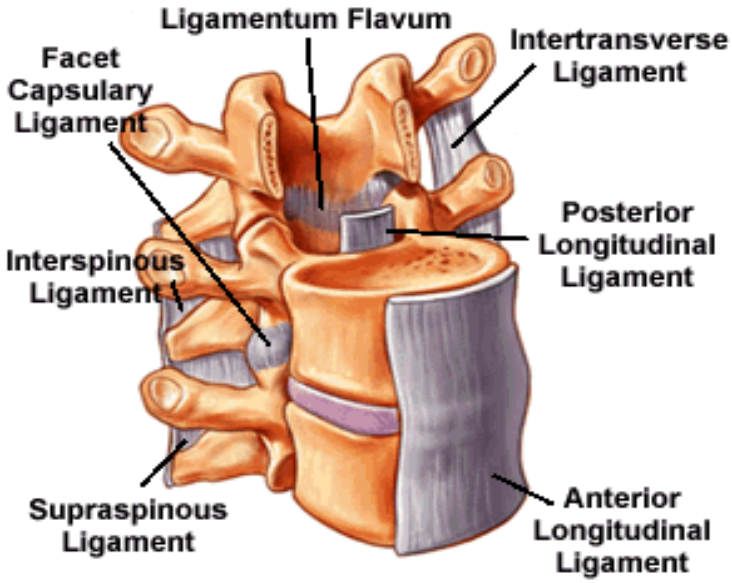
Vertebral column is bound together by ligaments (Fig 2.) for stability and elasticity.

Supraspinous ligament, a strong fibrous cord connecting the apices of spinous processes and it continues as the ligamentum nuchae.

Interspinous ligament: a thin membranous ligament, connects spinous processes, blend anteriorly with ligamentum flavum and posteriorly with supraspinous ligament.

Ligamentum flavum: comprises of yellow elastic fibres, connects the adjacent lamina. The ligament begins at the root of articular processes laterally and extends posteriorly and medially to the point where the laminae join and form the spinous process.

Longitudinal ligaments: There are two longitudinal ligaments - anterior and posterior, bind the vertebral bodies together.



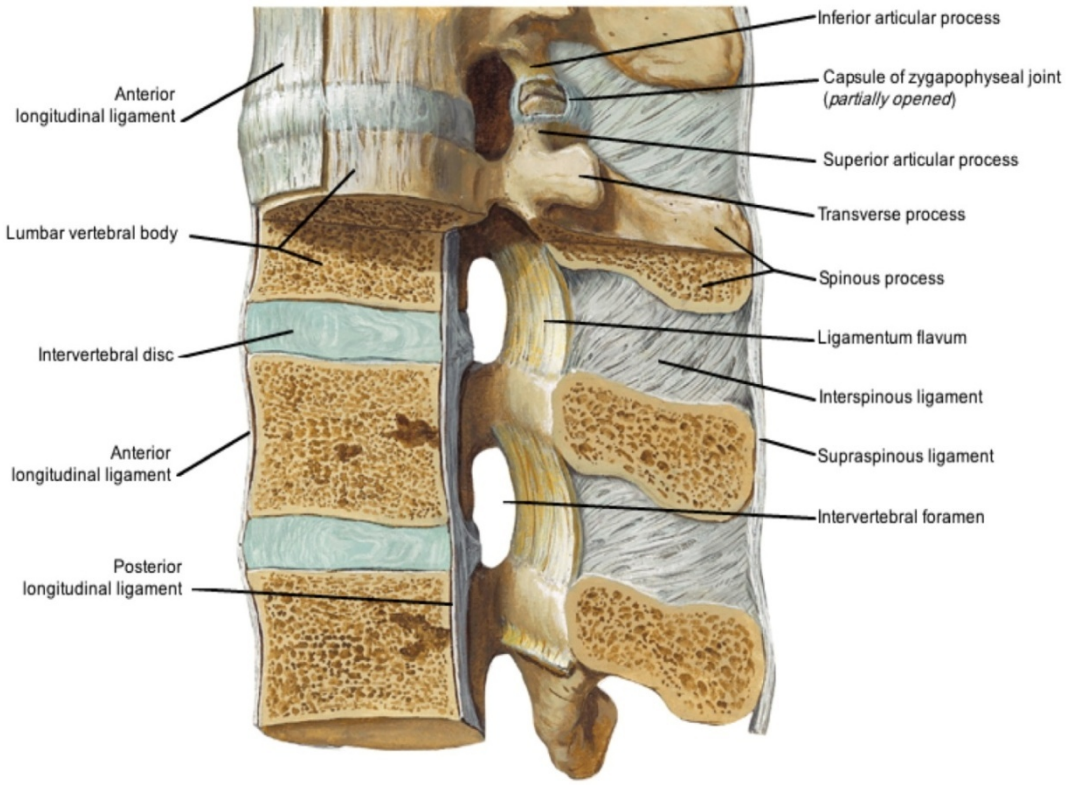


Figure 2. Vertebral Ligaments

Lumbar vertebrae[9] (Fig 3)

A lumbar vertebra has:

- A kidney shaped body.
- Two pedicles directed backwards from the upper part of the body.
- Two slender transverse processes.
- Two laminae meeting posteriorly and enclosing the triangular vertebral foramen.
- Thick, broad Spinous processes which are quadrilateral in shape.
- Two upper and lower articular processes - prevents rotation but allow limited flexion and extension between the contiguous vertebrae.

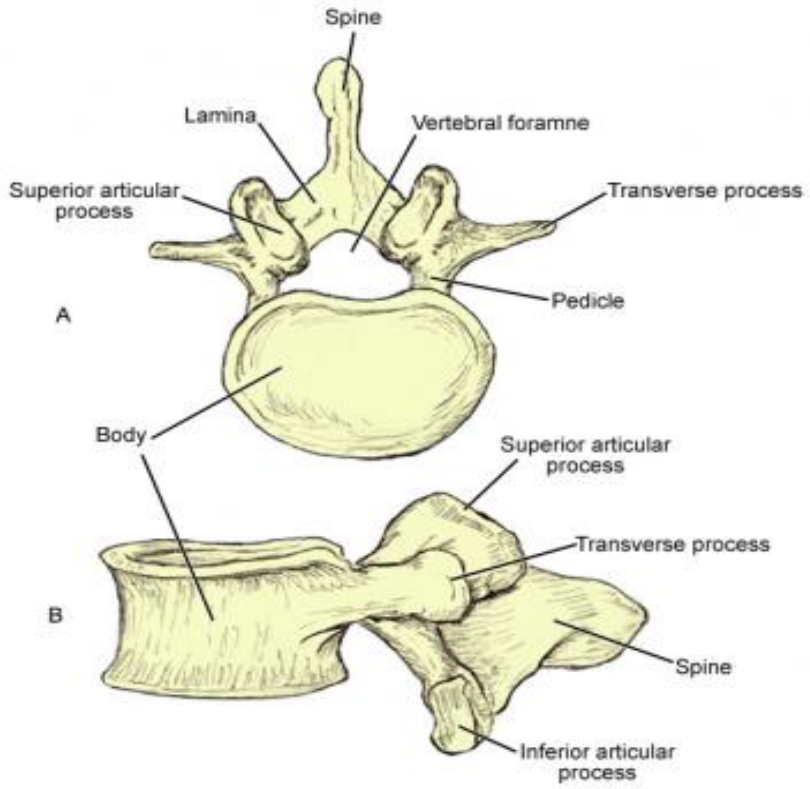


Figure 3. Lumbar Vertebra

Posteriorly vertebral canal is bounded by spinous processes and interspinous ligaments, by the pedicles laterally and by the laminae and ligamentum flavum posterolaterally. It extends superiorly from the foramina magnum and inferiorly ends in the sacral hiatus. It consists of the spinal cord, spinal membranes, adipose tissue, blood vessels, CSF and the roots of the spinal nerves.

SPINAL CORD[11]

The brainstem continues as the spinal cord below the level of foramen magnum and terminates distally in the conical extremity known as conus medullaris as the delicate fibrous filament - the filum terminale, which descends to the back of first segment of coccyx from apex of conus medullaris, and cauda equina. In adult males the average length of the spinal cord is 45cms and in females 42cms, terminates at the level of L3 at birth and gradually rises with the progressing age to reach the lower border of L1 in adults.

Blood Supply of Spinal Cord[11] (Fig. 4)

A single anterior spinal artery (branch of vertebral artery) and two posterior spinal arteries (branch of inferior cerebellar artery) and the segmental spinal arteries (branch of intercostal and lumbar arteries) form the blood supply for the spinal cord. The major branch of spinal arteries, artery of Adamkiewicz supplies the lower thoracic and upper lumbar regions. Anterior spinal artery lies in the substance of pia mater over the anterior median fissure and supplies the lateral and anterior columns, which forms three quarters of substance of the cord. Thrombosis of this artery causes anterior spinal artery syndrome. The pairs of posterior spinal arteries supply posterior column of the cord. Venous drainage from the neck drains into the plexus of anterior and posterior veins, from the thorax into the azygos veins,

from the abdomen into the lumbar veins and from the pelvis into the lateral sacral veins.

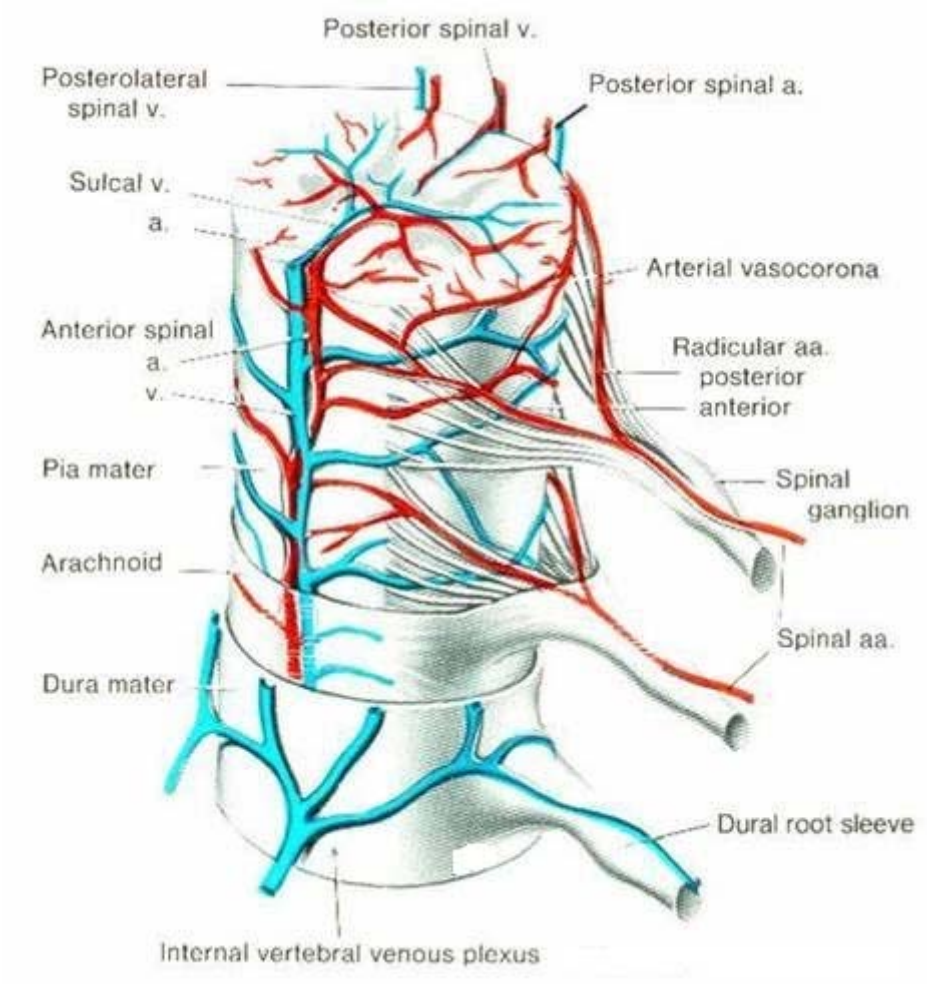


Figure 4. Blood Supply of Spinal Cord

Meninges[12]

Three connective tissue coverings – the meninges, also protects the spinal cord along with the bony vertebral column. **Duramater**[12]**,** the tough outermost fibro elastic covering with an outer endosteal and an inner meningeal layer. Fibres of dura run longitudinally, so while inserting the spinal needle it is important to insert it in a way it only splits these fibres and not cut them so as to prevent unnecessary leak of CSF and to prevent post dural puncture headache therewith). Dural sac terminates at the lower border of S2, where it is pierced by filum terminale. **Arachnoid Mater**[12] is a delicate, non vascular, middle covering closely attached to the dura, functions as a principal barrier to the drugs crossing in and out of the CSF. There is a *subdural space*, a capillary interval or a potential space between dura and arachnoid mater which contains serous fluid. **Pia Mater**[12] is the innermost membrane, a vascular sheath which closely covers the brain and spinal cord.

Subarachnoid Space or the Intrathecal space[12] is the space between the arachnoid and pia mater, filled with cerebrospinal fluid and is composed of numerous arachnoid trabeculae, a delicate sponge like mass.

Cerebrospinal Fluid[12]

It is a clear colourless fluid which resides in the space between the pia mater and the arachnoid mater, the cranial and spinal subarachnoid spaces and in the ventricles. Approximately 500ml of CSF is either secreted or formed by ultrafiltration from the choroidal plexus of the lateral ventricles per day, and is absorbed into the arachnoid granulations in the cerebral hemispheres.

Properties:

- Specific gravity: 1.003 to 1.009 at 37^0C.
- Volume: 500ml is produced per day (30-80ml occupies the subarachnoid space from T_1 to T_{12}).
- CSF pressure: 60 to 80 mmHg in lumbar space.
- pH : 7.27 to 7.37
- Composition: PCO_2 : 48 mmHg, HCO_3 : 23 mEq/L, Sodium : 135-145 mEq/L, Calcium : 2-3 mEq/L, Phosphorous : 1.6 mg/dl, Magnesium : 2-2.5 mEq/L, Chloride : 15- 20 mEq/L, Proteins : 23-38 mg/L

PHYSIOLOGY OF SUB ARACHNOID BLOCK

In spinal anaesthesia, the local anaesthetic agent is deposited in the subarachnoid space, following which the there is a readily appreciable loss of sensation and muscle paralysis which reflects the direct blocking effect on transmission of the spinal nerve fibre impulses. In order of importance there are three sites of action of local anaesthetic agents instilled in the intrathecal space:

- Primary - on the nerve roots of spinal cord.
- Secondary - on the dorsal root ganglion and posterior-anterior horn synapses.
- Limited and incomplete - on the spinal cord parenchyma in the ascending-descending tracts.

Factors affecting spinal blockade include[13]

- Type of drug.
- Volume of solution.
- Site of injection.
- Rate of injection.
- Specific gravity of solution - density and baricity.
- Barbotage.

Factors affecting spread of blockade includes[14]

1. Patient factors:
    - Age.
    - Height.
    - Position of the patient.
    - Spinal column configuration.
    - Cerebrospinal fluid volume.
2. Technical factors:
    - Site of injection.
    - Direction of bevel of the needle.
    - Local anaesthetic dose.
    - Local anaesthetic baricity.
    - Local anaesthetic volume.

The spinal nerve roots and the dorsal root ganglia are the principal sites of action. Nerves in the intrathecal space are highly accessible and easily anaesthetized, even with a small dose of local anaesthetic agent. The sensory and motor blockade reflects the direct effects of local anaesthetic on the spinal nerve roots. The smaller nerve fibers are affected first, and thick large motor fibers last. The sympathetic blockade is more diffuse and generally extends two to four segments above the level of motor blockade. The sympathetic blockade is first to occur and are last to recover and the motor nerve blockade is usually affected last and first to recover.

Sequence of spinal anaesthesia[15]

- Vasomotor block: Dilatation of skin vessels and increase in the cutaneous blood flow.
- Temperature fibers: the unmyelinated C fibers - Cold first and warmth later.
- Loss of temperature discrimination.
- Pain - pin prick fibers – the myelinated A-delta fibers.
- Loss of tactile sensation – the myelinated A-beta fibers.
- Motor paralysis – the myelinated A-alpha fibers.
- Pressure sensation.
- Proprioception and vibratory sensation.

Sympathetic blockade

The level of sympathetic denervation determines the magnitude of cardiovascular responses to subarachnoid block, the higher the level of neural blockade the greater the change in the cardio-circulatory parameters. In partial sympathetic blockade, there is a reflex increase in sympathetic activity in the sympathetically intact areas which causes vasoconstriction that tends to compensate for the peripheral vasodilatation in the sympathetically denervated areas.

EFFECT OF SUBARACHNOID BLOCK ON DIFFERENT SYSTEMS

Cardiovascular System[40]:

The effects of autonomic denervation with higher levels of neural blockade, and added effects of vagal innervations together mediate the changes in cardiovascular system, which includes:

- Fall in stroke volume
- Venous and arterial vasodilatation thereby reducing the preload (venous return) and afterload (systemic vascular resistance) respectively.
- Biphasic response in cardiac output – initial increase due to fall in systemic vascular resistance followed by eventual fall in cardiac output which reflects the block of cardiac efferent sympathetic fibres of T_1-T_4 causing loss of chronotropic and inotropic drive.
- Bainbridge reflex or the blockade of cardioaccelatory fibers from T_1-T_4 results in bradycardia.
- Systemic absorption of local anaesthetic causes depression of vascular smooth muscle and beta adrenergic blockade of myocardium resulting in fall in cardiac output.

Block extending above the level of T4 is associated with extensive fall in BP.[40] Bradycardia may also be due to lowering blood pressure in the right atrium owing to diminished venous return.

Theories behind the reasons for fall in BP are:-

- Diminished cardiac output following reduced venous return
- Dilatation of posterior arteries, capillaries and small venules.
- Sympathetic blockade of the nerve supply to heart.
- Sympathetic blockade of nerve supply to adrenal glands with consequent catecholamine depletion.
- Ischemia and hypoxia of vital centres.
- Compression of great vessels in abdomen by gravid uterus or intra abdominal tumors.

During hypotension associated with spinal anaesthesia there is decrease in myocardial oxygen demands owing to decrease in preload, afterload, and heart rate.

Cerebral Blood Flow

Cerebral blood flow (CBF) in humans is maintained at constant levels by cerebrovascular autoregulatory mechanisms. The spinal anaesthesia induced fall in blood pressure can decrease regional cerebral blood flow in elderly and patients with pre-existing hypertension.

Respiratory System

Paralysis of the abdominal muscles is followed by decrease in vital capacity from a reduction in expiratory reserve volume. Blockade of intercostal and abdominal muscles is compensated by unaltered function of diaphragm and the accessory muscles of respiration. The respiratory arrest

associated with spinal anaesthesia is related to hypoperfusion of the respiratory centres in the brainstem and not due to Phrenic or inspiratory dysfunction. During spinal analgesia due to motor blockade and differentiation with reduction of sensory input to the respiratory centre, breathing becomes quiet and tranquil. Lowered arterial and venous tone lowers the work of the heart and thereby relieves any pre-existing pulmonary congestion. The pulmonary gas-exchange is preserved.

Gastrointestinal System

Neuraxial blockade of T_6-T_{12} interferes with the splanchnic sympathetic innervations to the gastrointestinal tract leading to contracted gut and hyperperistalsis. Associated nausea and vomiting may be present owing to unopposed parasympathetic activity. Fall in hepatic blood flow parallels the fall in mean systemic arterial pressure which may affect the metabolism of amide anaesthetics. Subarachnoid block interrupt the hyperglycemic response to surgery and stress and hence is beneficial in diabetics, the response to insulin is enhanced and carries risk of hypoglycaemia[35].

Genitourinary System

There is a predictable decrease in renal blood flow due to hypotension, but is of little physiologic significance until mean arterial blood pressure has fallen to about 50mmHg. There could be spinal

anaesthesia induced urine retention which may last longer as the paralysis of the small S2 to S3 autonomic fibers lasts longer than that of larger sensory and motor fibers. Uterine tone is preserved. Block of nerves from T_{11} and downwards helps in painless labour. Spinal anaesthesia reduces the threshold for shivering.

ALPHA-2 ADRENOCEPTORS AND THEIR AGONISTS

Distribution of α_2-adrenoceptors

Presynaptic α_2-adrenoceptors (α_2-AR) located in sympathetic nerve terminals and noradrenergic neurons in the CNS block the release of noradrenalin. Postsynaptic α_2-AR are located in the peripheral nervous system, CNS, eye, liver, pancreas, kidney, platelets, and the adipose tissue.

The medullary dorsal motor complex which has a high population of α_2-AR, when activated they may probably be responsible for the blood pressure and heart rate effects of α_2-AR agonists.[17] Locus coeruleus is an important mediator of arousal and is the major site for the hypnotic action of α_2-AR agonists. [18]

The locus coeruleus has numerous efferent connections. The subthalamic relay nucleus and the thalamus influence the cortical activity via noradrenergic fibres. The descending fibres in the dorsolateral funiculus tracts are responsible for the decrease in nociceptive communication at the spinal level. Furthermore, there are efferent fibres to the reticular formation with links to the vasomotor centres, and there are afferent connections from

the rostral ventrolateral medullary nuclei as well. High concentrations of α_2-AR have been found in the vagus nerve, intermediolateral cell column and in substantia gelatinosa. α_2-A subtype adrenoceptors are found in the dorsal horn of the spinal cord whereas the primary sensory neurons contain both α_2-A and α_2-C adrenoceptors subtypes.

Physiology of the α_2-adrenoceptors

These are primarily located on the presynaptic membrane; they modulate the release of norepinephrine (NE), while postsynaptic adrenergic receptors mediate smooth muscle vasoconstriction. Postsynaptic α_2-AR is located in the peripheral nervous system, CNS, eye, liver, pancreas, kidney, platelets, and the adipose tissue. Quite recently, the predominant α_2-AR was identified in human spinal cord and was named α_2-AR subtype 3.

Responses mediated by a2-adrenergic receptors

Activation of the α_2-adrenoceptors in the brain and spinal cord inhibits neuronal firing, responsible for hypotension, bradycardia, analgesia, and sedation. Other effects include decreased salivation, decreased secretions, reduced bowel motility; smooth muscle contraction; inhibition of renin release, increased GFR, and increased secretion of sodium and water; decrease in intraocular pressure; and reduced insulin release from the pancreas.

PHARMACOLOGY OF ALPHA-2 RECEPTOR AGONISTS

Dexmedetomidine, a stereoisomer of medetomidine[19], an imidazole derivative, is a very specific and short acting α-adrenoceptor agonist with 1600 fold greater selectivity for α_2 over α_1 adrenoreceptors. The chemical name of Dexmedetomidine hydrochloride is (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride; and the empirical formula is $C_{13}H_{16}N_2$.HCL. (fig. 5).

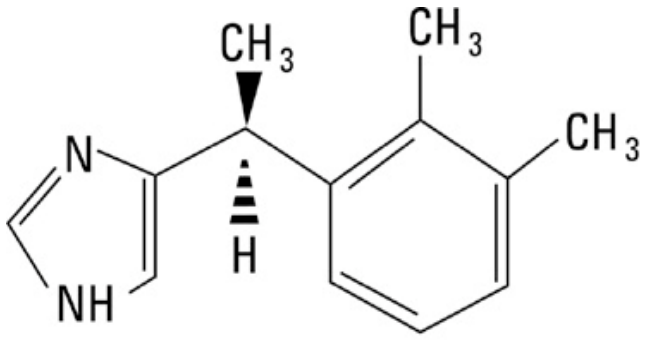


Figure 5. Structure of Dexmedetomidine

The current clinical indications of Dexmedetomidine include

- for ICU sedation in mechanically ventilated patients (for up to 24 hrs as continuous infusion)
- Perioperative sedation or for sedation during minimal invasive procedures.

The sedative dose is 1mcg/kg i.v bolus over 10 min followed by i.v infusion at the rate of 0.2 to 0.7 mcg/kg/hr.

Pharmacokinetics

- Volume of distribution of around 200L.
- Systemic clearance of 0.5 L/min after i.v infusion.
- Exhibits a concentration-dependent nonlinear pharmacokinetic profile. At high concentrations of intravenous bolus, there is decrease in the initial volume of distribution and intercompartmental clearance owing to its peripheral vasoconstrictive action.
- The drop in concentration of Dexmedetomidine results in vasodilatation due to its central effect (rapid administration of Dexmedetomidine can cause undesirable rise in blood pressure and altered pharmacokinetics).
- The drop in the plasma concentration of Dexmedetomidine is predicted by its context-sensitive half-life (intramuscular route offers better predictability, and has relatively rapid onset of action, the peak plasma concentration occur within 15min[20].

Mechanism of action (fig.6)

Presynaptic α_2-AR controls the release of norepinephrine and adenosine triphosphate (ATP) through a negative feedback mechanism. In short, presynaptic activation of the α_2-AR inhibits the release of norepinephrine, terminating the dissemination of pain signals while postsynaptic activation of α_2-AR inhibits sympathetic activity and thereby can decrease blood pressure and heart rate. These effects compiled provide analgesia, sedation, and anxiolysis thus avoiding the need for multiagent therapies[22].

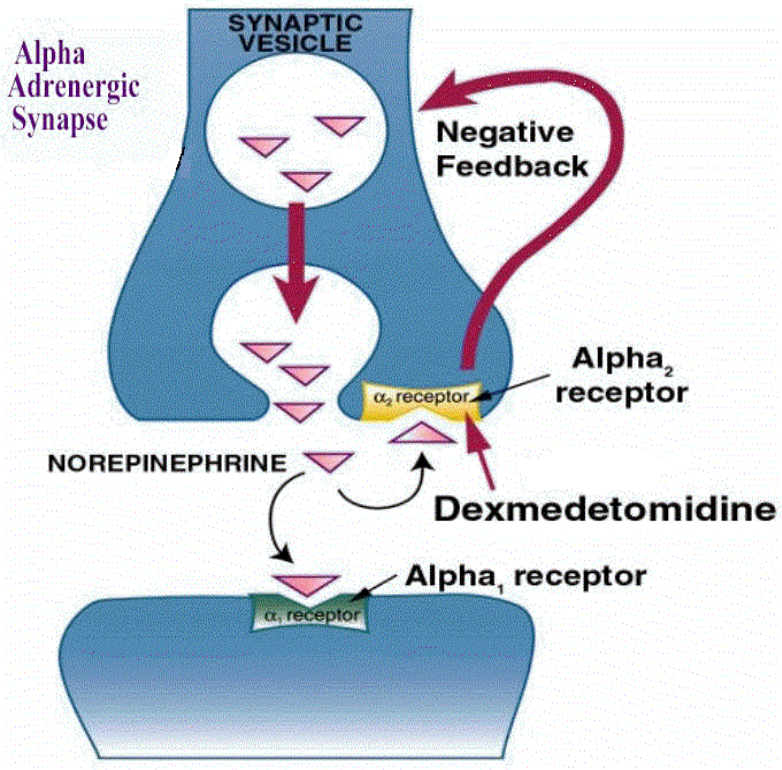


Figure 6. Mechanism of action of Dexmedetomidine

PHARMACODYNAMICS

Dexmedetomidine is a complete α_2-adrenoceptor whereas clonidine is a partial α_2-adrenoceptor agonist. The selectivity of Dexmedetomidine over clonidine to α_2-adrenoceptor is 1620:1 and 200:1 respectively. The selectivity is dose dependant, i.e., at low to medium or on slow infusion, high α_2-selectivity is observed, whereas on high doses or rapid infusions of low doses were found to have both α_1- and α_2- activities.[22]

Effects on CNS

Dexmedetomidine provides dose dependant anxiolysis and sedation. Arousability is maintained even at deep levels of sedation with good association between the level of sedation and the bispectral EEG. Dexmedetomidine induces sleep by activating intrinsic non-rapid eye movement pathways. Activation of α_{2A}-receptors in the locus coeruleus inhibits noradrenergic neurons.

Ramsay et al[24] evaluated Dexmedetomidine sedation of 401patients in the post operative period. Dexmedetomidine or saline was administered on arrival in the intensive care unit at 1.0 mcg/kg for 10 minutes, later titrated to 0.2 to 0.7 mcg/kg/hr to effect. Patients could be given propofol if necessary. Morphine was administered as analgesic – 60% of the patients who received Dexmedetomidine required no other sedative to maintain a Ramsay sedation score $\geq$ 3; 21% required < 50 mg of Inj. Propofol. In contrast, 76% of the patients in control group received propofol; of which 59% required $\geq$ 50 mg of Propofol. Patients who received Dexmedetomidine

required significantly lower doses of morphine for pain relief ($p<0.001$). Continuously given throughout the ICU stay, Dexmedetomidine had no ventilatory depressive effects. Dexmedetomidine patients barely remembered pain or discomfort and majority of the patients maintained blood pressures within normal limits, without rebound hypertension.[24]Atelectasis, and rigors were observed to be more frequent in the control group.

Dexmedetomidine was observed to decrease cerebral blood flow in dogs due to its interaction with halothane and isoflurane, with no sign of global ischaemia, it had only mild effect on ICP and has been shown as neuroprotective in animal models of brain ischemia.[25] In animal models of incomplete cerebral ischemia and reperfusion Dexmedetomidine was found to minimize cerebral necrosis and improve neurologic outcome. It was shown that decrease in the intracerebral catecholamine outflow following injury resulted in less neural tissue damage with more desirable neurologic outcome.

The hypnotic and supraspinal analgesic action of Dexmedetomidine are regulated by the hyperpolarisation of noradrenergic neurons, leading to stimulation of K^+ channel, Ca^{2+} inhibition, inhibition of adenylcyclase which subdue neuronal firing in the locus coeruleus along with inhibition of norepinephrine release and its effect on the descending medullo-spinal noradrenergic pathway, secondary to activation of central α_2-AR s. This in turn triggers neurotransmitters that reduce the histamine secretion providing

hypnosis similar to normal sleep, (with no ventilatory depression), making Dexmedetomidine a near ideal sedative agent. Subdued activity in the descending noradrenergic pathway, which mediates nociceptive neurotransmission, terminates the propagation of pain signals leading to analgesia.[26]

Mechanism of analgesia

α_2-receptor agonists demonstrate analgesic effect when administered via the intrathecal or epidural route. The primary site of action is thought to be at the spinal cord. Narcotic sparing is observed with systemic use of Dexmedetomidine[26]. Dexmedetomidine restrain the release of substance P from the dorsal horn of the spinal cord, which is also responsible for primary analgesic effects.[22] Dexmedetomidine has an inhibitory action on the locus coeruleus (A6 group) present at the brain stem. The prolongation of spinal anaesthesia is indicative of the supraspinal action of Dexmedetomidine when given intravenously. The noradrenergic innervation of the spinal cord emerges from the noradrenergic nuclei present in the brain stem which also includes the locus ceruleus, the A5, and the A7 noradrenergic nuclei. Neurons in the locus ceruleus are linked to the noradrenergic nuclei. The noradrenergic axon terminals reach lamina VII and VIII of the ventral horns of the spinal cord. The activity of the noradrenergic neurons is reduced by agonists acting at α_2-AR on the locus ceruleus. Therefore, inhibition of the

locus ceruleus activates the noradrenergic nuclei and produce descending inhibitory effect on nociception.[22]

[27]Al-Mustafa MM et al conducted a study on the effect of adding Dexmedetomidine to bupivacaine for neuraxial anaesthesia, 66 patients were randomly assigned into 3 groups, and each group received intrathecal bupivacaine 12.5mg, combined with normal saline for the patients allotted in group N, Dexmedetomidine 5 mcg in group D5, and Dexmedetomidine 10 mcg in group D10. The mean time taken for the level of sensory block to reach T10 dermatome was 4.7 +/- 2.0 minutes in D10, 6.3 +/- 2.7minutes in D5 group, and 9.5 +/- 3.0 minutes in group N patients. The mean time to reach modified Bromage scale value 3 was found to be 10.4 +/- 3.4 minutes in D10 group of patients, 13.0+/- 3.4 minutes in D5 group, and 18.0 +/- 3.3 minutes in group N patients. The regression time to reach S1 dermatome was 338.9 +/- 44.8 minutes in D10 group of patients, 277.1 +/- 23.2 minutes in D5 group, and 165.5 +/- 32.9 minutes in group N patients. The regression to Bromage 0 was observed to be 302.9 +/- 36.7 minutes in D10 group of patients, 246.4 +/-25.7 minutes in D5 group, and 140.1 +/- 32.3 minutes in group N patients. Onset and regression of sensory and motor block were significantly raised (N v/s D5, N v/s D10, and D5 v/s D10, $p<0.001$. It was concluded that, Dexmedetomidine has effects on the onset and regression of sensory and motor block which is dose dependant when used as an adjuvant to bupivacaine in subarachnoid block.

Eid HEA et al conducted a study on 48 adult patients posted for anterior cruciate ligament reconstruction surgery; the patients were randomized into three groups. Each patient was given 3.5ml of 0.5% hyperbaric bupivacaine and 0.5ml containing either Dexmedetomidine 10mcg (group D1), Dexmedetomidine 15mcg (group D2) or normal saline (group B). It was observed that intrathecal Dexmedetomidine in doses of 10 mcg and 15 mcg significantly prolonged anaesthetic and analgesic effect of spinal hyperbaric bupivacaine in a dose dependent manner.

A study[24] was performed to assess the effects of intravenous Dexmedetomidine on low dose bupivacaine spinal anaesthesia in geriatric age group. Fifty one elderly patients undergoing TURP were randomized into two groups who received either 1.0mcg/kg Dexmedetomidine (group D, n=26) or normal saline (control group, n=25) i.v prior to spinal anaesthesia with 1.2 ml of 0.5% bupivacaine. The mean time for two segment regression (39 min v/s 78min for cold, 41min v/s 61 min for pinprick) and that for motor regression (23 min Vs 46 min) were longer in patients belonging to group D than in the control group. The atropine - requiring bradycardia was observed more frequent in the D group (24.0% Vs 3.8%).The median sedation score ranged from 4 (2¬6) in the D group and 2 (1-3) in the control group (p,0.001) intraoperatively. Two patients in the group D showed peripheral oxygen desaturation of <90% intraoperatively. The duration of post-operative anaesthesia care unit stay was longer in the group D than in the control group (58 min Vs 96 min). Postoperative pain severity was lower

and the average time to first request for post operative analgesia was delayed in the group D compared to the control group (6.6 hr v/s 2.1 hr). It was concluded that iv Dexmedetomidine prolonged the time span of spinal anaesthesia and refined post-operative analgesia. However, more intense sedation with desaturation was observed with bradycardia occurring more frequently, and delayed recovery had to be anticipated in elderly patients.

Effect on Sleep

The α_2-AR acts through the intrinsic sleep promoting pathways so as to produce their sedative effects. It provides a unique sedative quality described as "Clinically sedated yet arousable". Despite sound levels of sedation with the administration of Dexmedetomidine there was no respiratory depression providing a wide safety margin.[30]

Effects on CVS

Both α_1- and α_2- post junctional receptors exist in arterial as well as venous vasculature where they both cause vasoconstriction. The α_1- and α_2-adrenoreceptors has diverse location, and utilisation of calcium. In the arterial vasculature, the α_1-AR are junctional whereas the α_2-AR are extra-junctional, and vice versa in venous vasculature. α_1-adrenoceptor activation produces vasoconstriction by using intracellular Ca^{2+} while the α_2-AR controlled vasoconstriction utilizes extracellular Ca^{2+}. This ensures that the

pressor response of α_2-adrenoceptor agonists' are more sensitive to calcium antagonists.

Intravenous α_2-adrenoceptor agonist administration causes decrease in heart rate as well as transient rise in arterial blood pressure and systemic vascular resistance, but results in a decreased cardiac output owing to the activation of postjunctional vascular α_2-AR. This is followed by a longer lasting reduction in both heart rate and blood pressure due to a centrally mediated reduction in sympathetic tone and an increased vagal activity. Neither an exact location nor the exact receptors responsible for the central hypotensive action of α_2-AR agonists have been discovered yet. Theories proposed that postsynaptic α_2-AR and imidazoline receptors in the brainstem are involved.[22]

The bradycardia commonly observed following administration of α_2-AR agonists may be a result of the central sympatholytic action of these drugs leaving an unopposed vagal tone. It can also be indicative of presynaptic-mediated reduction of norepinephrine release or a direct vagomimetic action.[22]

Although bradycardia can be an issue with the administration of α_2-AR agonists, Dexmedetomidine has been shown to be protective against adrenaline-induced arrhythmias during halothane anaesthesia in dogs. This anti-arrhythmic action is supposedly due to activation of imidazoline receptors.[30] α_2-AR are not known to cause any direct effects on the myocardium. α_2-AR mediated decrease in sympathetic tone and increase in

parasympathetic tone is responsible for reduced heart rate, systemic metabolism, myocardial contractility and systemic vascular resistance. In short, the myocardial oxygen requirements are reduced.

Various studies reveal that the hypotension and bradycardia are produced when Dexmedetomidine is used as an adjuvant in spinal or general anaesthesia in normal doses, but is usually clinically insignificant.

Effect on Respiratory System

α_2-AR seems to yield minimal effects on ventilation. Clonidine in doses up to 300 mcg seemed to lessen the resting minute ventilation and increase end tidal carbon dioxide. [31]

Dexmedetomidine has a biphasic effect on respiratory drive, low doses decrease and higher doses increase the resting minute ventilation. Dexmedetomidine in doses up to 2 mcg/kg produced mild ventilatory depression, but this was not significantly different from that observed with placebo.[32]

The locus coeruleus is a key site for the action of α_2-AR agonists. The locus coeruleus is involved in arousal response; therefore suppression of its activity by α_2- AR agonists can cause a state similar to sleep with slight respiratory depression. α_2-AR stimulation has no remarkable effect on hypoxic or hypercapnoeic ventilator drives. Similarly the combination of α_2-AR agonists with opioids does not cause further ventilatory depression.

Effects on Renal System

Activation of α_1-AR in the kidney causes redistribution of blood from the cortical to medullary areas owing to the increase in renal vascular resistance. Stimulation of α_2-AR results in numerous effects that promote diuresis and natriuresis. They reduce the secretion of vasopressin and antagonises its activity on renal tubules. α_2-AR are also believed to inhibit the release of renin and increase the release of atrial natriuretic factor.[33]

Neuroendocrine System Effects

The α_2-AR agonists causes neuroendocrine responses mainly related to their inhibition of sympathetic outflow and therefore decreases the plasma levels of circulating catecholamines. Activation of α_2-AR located on the beta cells of the islets of Langerhans causes short term direct inhibition of insulin release and clinical hyperglycaemia. α_2-AR agonists also enhance the release of growth hormone and inhibit adipose tissue lipolysis.[34]

Effects on GIT

α_2-AR control vagally mediated increases in gastric and intestinal motility and secretions. Stimulation of α_2-AR inhibits water secretion as well as increases net absorption in the large bowel. For the same clonidine has been used to successfully treat diarrhoea. Stimulation of α_2-AR reduces salivary secretions which can cause dry mouth and patient discomfort.[35]

Effects on Platelets

Selective α_2-AR agonists are known to cause platelet aggregation by stimulating α_2-AR on platelets which requires high concentrations of α_2-AR agonists, low concentrations decrease plasma adrenaline concentration. The net response may be a reduction in platelet aggregation. α_2-receptor stimulation also causes release of nitric oxide, a potent inhibitor of platelet aggregation.[36]

DRUG AND RECEPTOR INTERACTIONS

α_2-AR agonists and opioids are noted to share similar pharmacological effects, they have similar distribution in the brain and that they acts by the activation of the same transduction and effector mechanisms - G- proteins and potassium channel coupling. Hence, if α_2-AR agonists and opioids are administered together they may display a synergistic action. It helps reduce the opioid dose requirement and decrease the respiratory and addictive side-effects therewith.[37]

α_2-AR agonists also share a synergistic action with benzodiazepines. Administration of verapamil, a calcium channel blocker prolong the duration of the hypnotic action of Dexmedetomidine, which reflects the reverse effect following the administration of a calcium antagonist.

BUPIVACAINE

Pharmacology [53-56]

Classification: aminoamide local anaesthetic

Chemical name: 1-butyl 2-piperidyl formo - 2'6'- xylidine hydrochloride.

It was first synthesized by a Swedish investigator Boaf Ekenstam.

Structure-Activity Relationships

Bupivacaine has an amide bond (-NHC-) between the hydrophilic hydrocarbon chain (which makes it water soluble) to the lipophilic aromatic ring (responsible for nerve penetration). Bupivacaine is available as racemic mixtures of S and R enantiomers and they totally differ in their pharmacologic profiles. (Ehlrich,1992).

Mechanism of Action

Mechanism of action of bupivacaine is similar to other local anaesthetics. The primary site of action is on the axon cell membrane on which it produces electrical stabilization and thereby prevents the large temporary increase in sodium ion permeability necessary for the propagation of the impulse, the resting membrane potential is preserved and inhibits depolarization in response to stimulation. There is an initial rise in the threshold for electrical excitation, the rate of rise of action potential is reduced and conduction slowed. In the due course propagation of the impulse fails.

The mechanism by which local anaesthetics block sodium conductance:

- Local anaesthetics in their cationic form act on the receptors within the sodium channels in the cell membrane and block it. The local anaesthetic gain access to the sodium channel either via the lipophilic pathway directly across the lipid membrane, or via the axoplasmic opening. This mechanism is responsible for 90% of the nerve blocking effects of amide local anaesthetics.
- The second mechanism of action is the membrane expansion which is a nonspecific action and is in contrast to the more specific drug - receptor interaction.

DOSAGE

As with all local anaesthetics the variation in the dosage of bupivacaine depends upon:

- Area to be anaesthetized.
- The vascularity of the tissue to be blocked.
- The number of neuronal segments to be blocked.
- Individual tolerance.
- Technique manifested.

Pharmacokinetics

Bupivacaine is a weak base with a Pk of 8.1, but is commercially available as acidic solutions in order to make it more water-soluble. The clinically used intrathecal solution of 0.5% Bupivacaine also contains 8.25%

Dextrose which makes it a hyperbaric solution. The pH is around 5.5 and it has a specific gravity of 1.0227-1.0278. When the pH of the local anaesthetic solution is close to its Pk value, it makes the solution more unionized and lipid soluble which provides a faster onset of action. So, commercially available 0.5% hyperbaric Bupivacaine solution usually has a slow onset of action. Once vascular absorption occurs, it gets distributed in the vessel rich group of tissues initially, followed by distribution in the skeletal muscles and fat.

- It is later Metabolized and eliminated by the liver.
- Bupivacaine is 95% protein bound -mainly alpha-1 glycoprotein.
- Volume of distribution is 73 L
- Clearance 0.47 L/min
- Elimination half time is 210 minutes (longer duration of action).

Metabolism

Possible pathways of metabolism include aromatic hydroxylation-dealkylation, amide hydrolysis and conjugation. (Pihlajamaki et al;1990).

Side Effects

- Allergic reactions
- Systemic toxicity
    - CNS toxicity (>4mcg/ml)
    - CVS toxicity (>8mcg/ml)

- Others - transient radicular irritation, Cauda equine syndrome and anterior spinal artery syndrome.

Uses of Bupivacaine:

- Local infiltration at the site of wound.
- Peripheral nerve blocks.
- Epidural analgesia/anaesthesia.
- Intrathecal anaesthesia.

MATERIALS AND METHODS

STUDY DESIGN

A quasi interventional study.

STUDY PERIOD

One year from September 2014 to September 2015

STUDY POPULATION

Patients posted for lower abdominal and lower limb surgeries.

STUDY SETTING

Department of Anaesthesia, Sree Mookambika Institute of Medical Sciences, Padanilam, Kulasekharam, Kanyakumari District.

INCLUSION CRITERIA

- Patients giving valid consent.
- Patients belonging to American society of anaesthesiologist (ASA) grade 1 or 2.
- Patients posted for elective lower abdominal or lower abdominal surgeries under Bupivacaine spinal anaesthesia.
- Patients aged between 20-60 years of age.

EXCLUSION CRITERIA

- Patient refusal.
- Patients with ASA grade 3 or more.
- Patients posted for emergency surgeries and caesarean section.
- Patients with history of alcohol/drug abuse.
- Patients with known allergy to test drug.

- Patient with known contraindication to spinal anaesthesia (coagulopathy, infection at puncture site, pre-existing neurological deficits in lower extremities.

SAMPLE SIZE

Sample size was calculated using the formula

$$(Z_{\alpha}+Z_{1-\beta})^2 (\sigma_1^2+\sigma_2^2) \div(\mu_1-\mu_2)^2$$

$$(Z_{\alpha}+Z_{1-\beta})^2=7.9$$

σ_1^2 = standard deviation 1=31.5[1]

σ_2^2 = standard deviation 2=34.8

μ_1= mean 1=190.1

μ_2=mean 2=165.2

Calculated sample size=28

Approximated sample size for the study=30

STUDY METHOD

After approval by the institutional ethical committee, ASA grade 1 and 2 patients of either sex, aged between 20-60 years of age, weighing 50-70kgs, posted for elective lower abdominal or lower limb surgeries, who met the inclusion criteria were enrolled for the study with written informed consent.

Patients with history of alcohol or drug abuse, diabetes mellitus, cardiac issues, hypertension, COPD, psychological disorders, hepatic and/or renal disorders, spinal deformities or any contraindication to spinal

anaesthesia – patient refusal, coagulopathy, infection at the site of puncture, pre-existing neurological deficits, were excluded from the study.

Patients were divided into two groups on an alternate basis – Group D – the study group and Group C – the control group. All the patients were visited on the previous day of the surgery and explained in detail about the anaesthetic procedure, reassured and written informed consent taken. The patients were kept nil per oral 6hrs prior to surgery. On arrival to the premedication room 18G venous cannula was secured and all the patients were prehydrated with 500ml of lactated Ringer's solution. Theatre was set ready with the necessary drugs including the emergency drugs, airway devices, defibrillator and other equipments. Standard monitors – continuous ECG, non-invasive blood pressure and pulseoximeter (SPO_2) and capnography were attached and baseline parameters recorded.

Preparation of the study drug

1ml of Dexmedetomidine (DEXTOMID * 1mL containing 100mcg of Dexmedetomidine) was diluted to make up a total of 10mL with sterile water making it 10mcg of Dexmedetomidine per cc, and required amount of the drug according to 0.5mcg/kg dose was loaded in a 20cc syringe and diluted again to make up a total of 10mL with sterile water for iv bolus infusion over 10 minutes.

Premedication for patients in Group D, included Inj. Ranitidine 50mg iv, Inj. Metoclopramide 10mg iv and Inj. Dexmedetomidine, 0.5mcg/kg which was diluted to make up a total of 10ml with sterile water and infused

intravenously over 10mins with the aid of an infusion pump half an hour before surgery, whereas patients in Group C received 10ml of normal saline intravenously instead of Dexmedetomidine over 10mins. The patients were positioned lateral decubitus and dural puncture performed at L3-L4 interspace through midline approach with 25 G Quincke needle, 15mg (3mL) of 0.5% Hyperbaric Bupivacaine was injected intrathecally and were immediately positioned supine for the surgery. All the patients received oxygen at a flow rate of 4L/min throughout the procedure.

OUTCOME VARIABLES

Sensory blockade

Sensory blockade was assessed using cold iced tube in the midaxillary plane every 2 minutes up to 10 minutes and thereafter every 10 minutes from the time of spinal block till 2 dermatome regression was achieved.

Recovery time for sensory blockade was defined as two dermatome regression of anaesthesia from the maximal level of block.

Motor blockade

Motor blockade was assessed by Modified Bromage scale[50]immediately after sensory block assessment every 2 min for first 10 minutes and every 10 minutes intra- and postoperatively.

- Modified Bromage scale 0 - no paralysis.
- Modified Bromage scale 1- unable to raise extended leg.
- Modified Bromage scale 2 - unable to flex knee.
- Modified Bromage scale 3 - unable to flex ankle.

Duration of motor block was considered as time for return to Modified Bromage scale 1.

Sedation

Sedation was assessed using Ramsay sedation score[51]at 10, 30, 50, 70, 90, 110 and 120 minutes.

- 1 - conscious or agitated.
- 2 - cooperative or tranquilized.
- 3 - drowsy but respond to command.
- 4 - asleep but respond to glabellar tap.
- 5 - asleep with sluggish response to tactile stimulus.
- 6 - asleep and no response.

Ramsay sedation score of 4 or more was considered excessive.

Hemodynamic parameters

The heart rate(HR),mean arterial blood pressure(MAP), peripheral oxygen saturation(SpO_2),end tidal CO_2 (ETCO2), respiratory rate(RR) were recorded before premedication, 2mins after premedication, before and after intrathecal block and every 5mins for 2hrs thereafter.

Fall in MAP below 20% of baseline or a systolic pressure less than 90mmHg was considered as hypotension for the purpose of the study and was treated with incremental doses of Inj. Ephedrine and a bolus administration of 250ml RL over 10 minutes.

Heart rate below 50bpm was considered bradycardia and was treated with 0.6mg Inj. Atropine iv. $EtCO_2$ in excess of 50mmHg or respiratory rate below 12 breaths per minute was considered respiratory depression.

Time to request for rescue analgesia

Postoperative pain was measured using Visual Analog Scale(VAS). VAS of 'zero' to 'ten' where 'zero' indicated no pain and 'ten' indicated worst imaginable pain. Inj. Tramadol 50 mg iv was given for rescue analgesia if the VAS score was more than 3.

DATA ANALYSIS

Data obtained was coded and entered into Microsoft excel. The categorical data expressed in terms of rates, ratios and percentage and continuous data expressed as mean ± standard deviation (SD). Statistical Package for Social Sciences (SPSS 16.0) is used for the statistical analysis of the present study. Unpaired sample 't' test is applied to find the statistical significant between the two groups. p value less than 0.05 ($p<0.05$) is considered statistically significant at 95% confidence interval. The datas are expressed in number, percentage, mean and standard deviation.

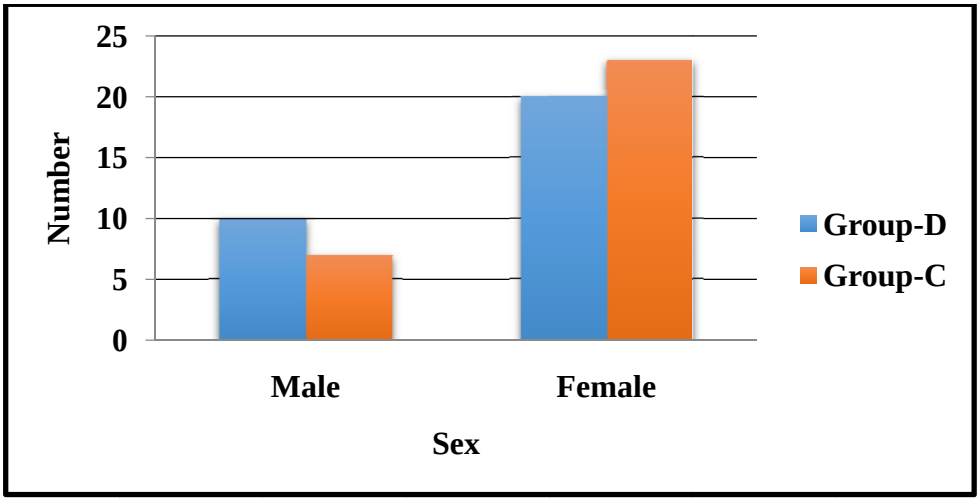
ANALYSIS AND INTERPRETATION

Statistical analysis: Statistical Package for Social Sciences (SPSS 16.0) is used for the statistical analysis of the present study. Unpaired sample t test is applied to find the statistical significant between the two groups. p value less than 0.05 ($p<0.05$) is considered statistically significant at 95% confidence interval. The datas are expressed in number, percentage, mean and standard deviation.

Table 1. Sex Distribution

Gender	Group D		Group C		Total	
	N	%	N	%	N	%
Female	10	33.33	7	23.33	17	28.33
Male	20	66.67	23	76.76	43	71.67
Total	30	100	30	100	60	100.0

Graph-1: Sex Distribution



In the present study 33.3% in Group D were females and 66.7% males whereas in Group C 23.33% females and 76.76% were males. The demographic status is comparable in both the study groups.

Table 2. Age Distribution

Age	Group D		Group C		Total	
	N	%	N	%	N	%
<30	8	26.67	6	20.00	14	23.33
31-40	6	20.00	12	40.00	18	30.00
41-50	9	30.00	9	30.00	18	30.00
51-60	7	23.33	3	10.00	10	16.67
Total	30	100.0	30	100.0	60	100.0

Graph-2: Age distribution

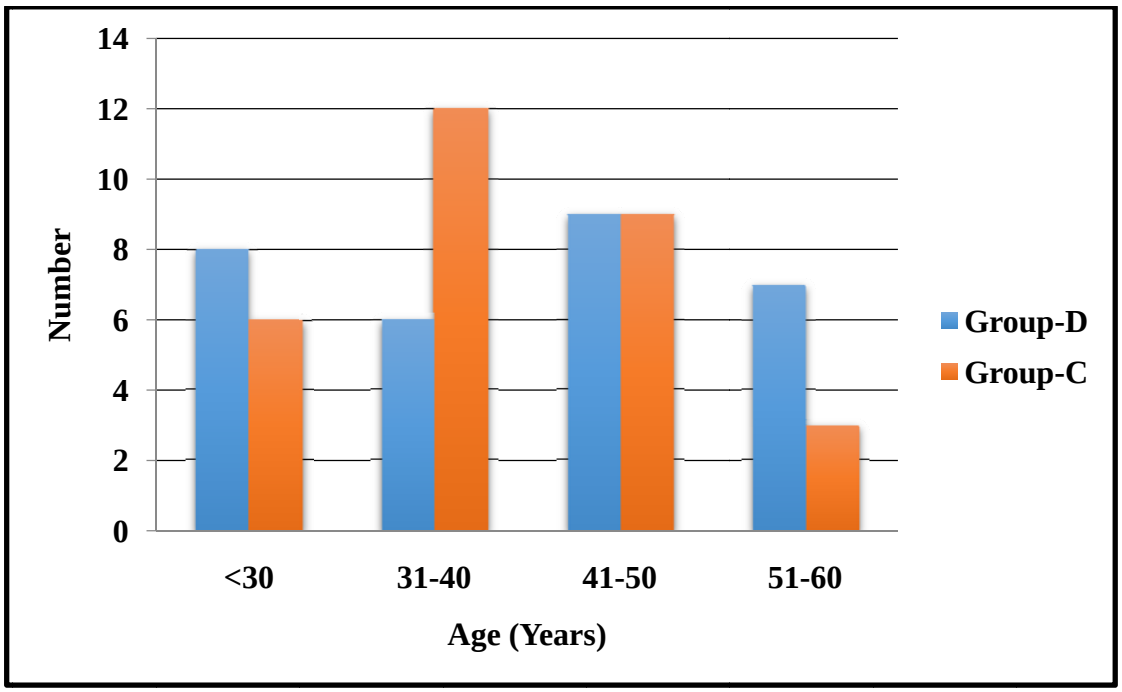


Table-3: Comparison of mean age in group D and C

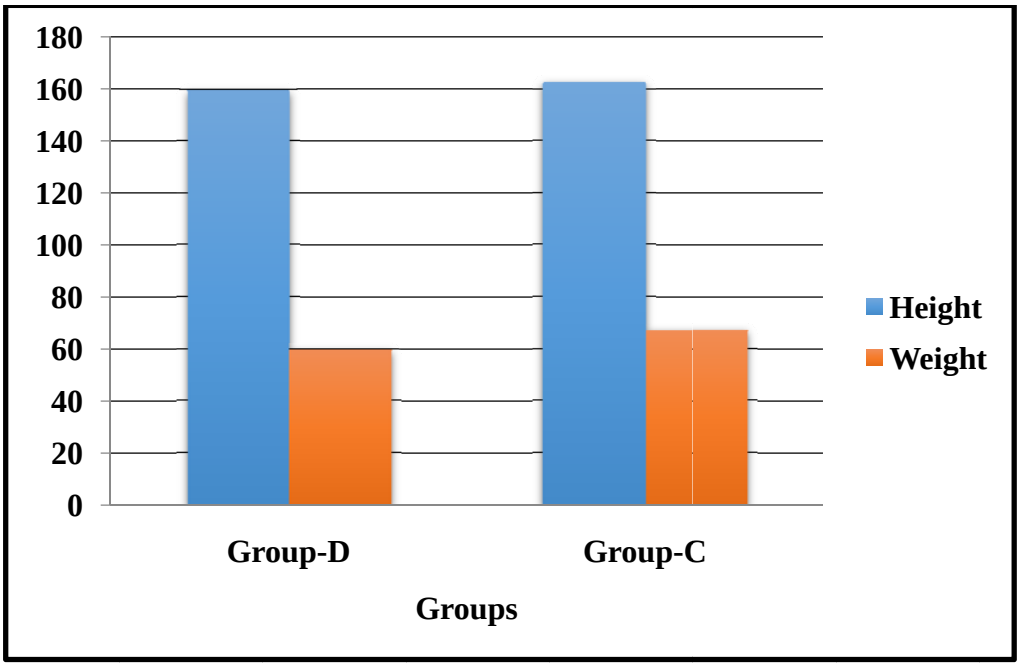
Category	N	Age in years		t	p
		Mean	sd		
Group	30	39.93	1.07	0.56	0.57
Group	30	38.46	9.16		

In both the groups majority of the patients belonged to age group between 31-50 years and the mean age in group D was 39.93 and 38.46 in group C. Both the study groups were comparable with respect to the demographic variables, p = 0.57.

Table-4: Mean height and weight

		N	MEAN	sd	t	p
Height	**Group D**	30	159.60	5.39	-1.91	0.06
	Group C	30	162.60	6.68		
Weight	**Group D**	30	59.93	5.92	-5.56	0.001
	Group C	30	67.23	4.05		

Graph-3: Mean height and weight

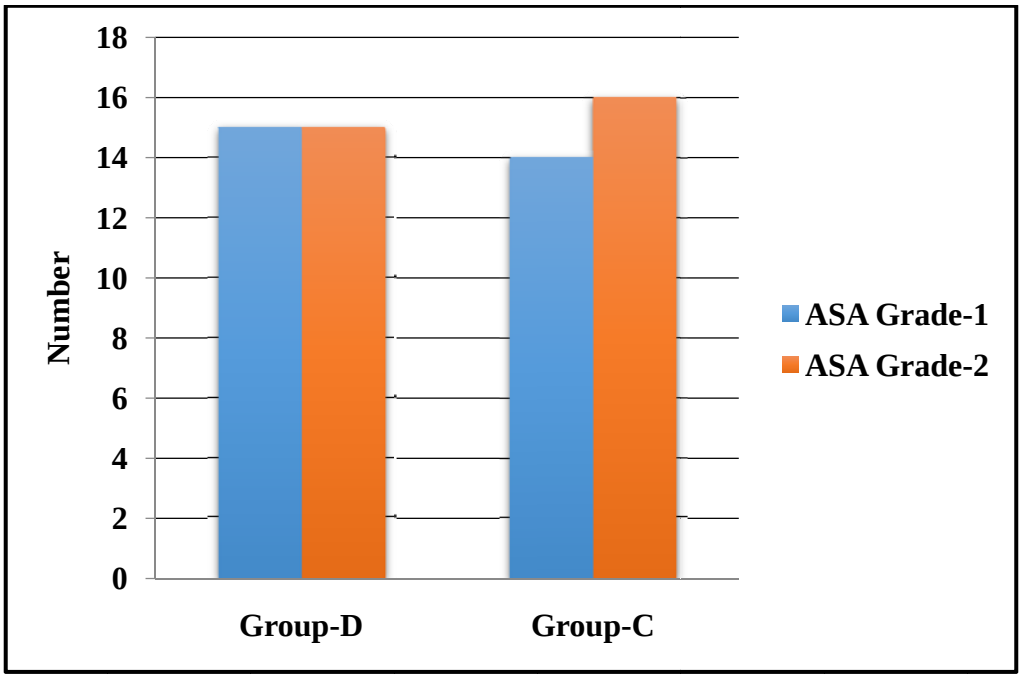


The mean height in group D was 159.60±5.39 and that in group C 162.60±6.68. The mean weight was 59.93±5.92 in group D and 67.23±4.05 in group C. Data suggests that both the study groups were comparable considering mean height and weight of the patients. (p =0.06 and 0.001 respectively).

Table-5: ASA grade

ASA grade	GROUP D		GROUP C		TOTAL	
	N	%	N	%	N	%
1	15	50.00	14	46.67	29	48.33
2	15	50.00	16	53.33	31	51.67
Total	30	100.0	30	100.0	60	100.0

Graph-4: ASA grade

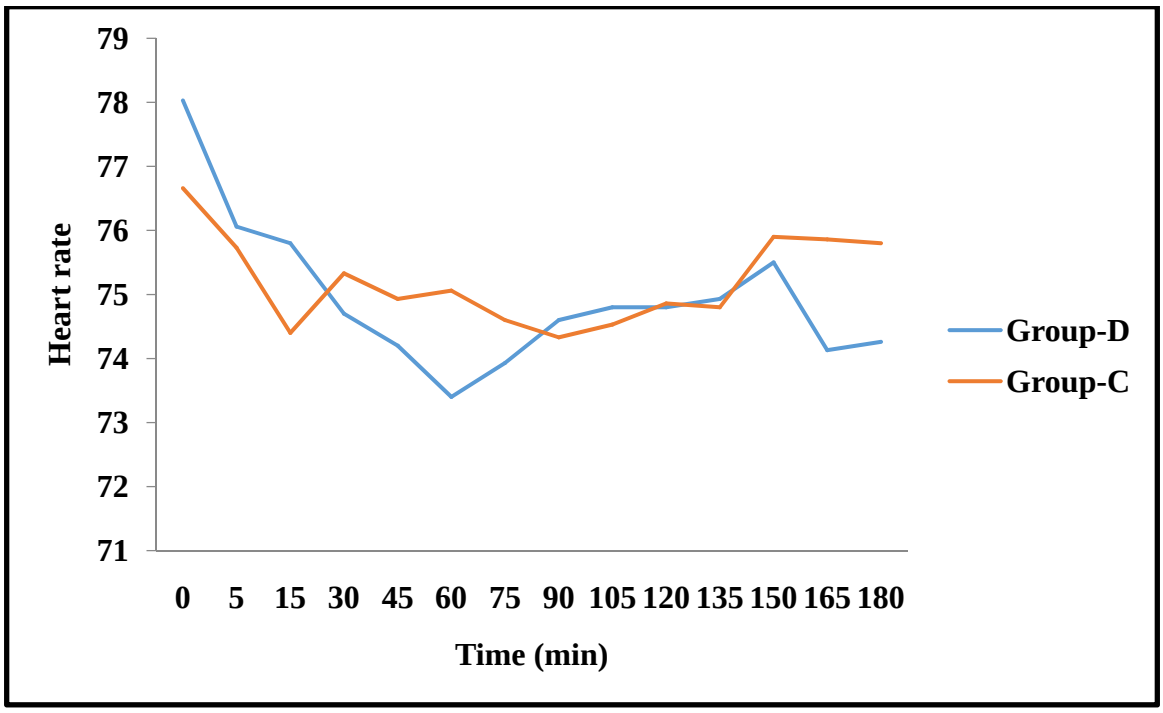


In group D 50% of the patients were ASA 1 and 50% ASA 2, whereas in group C 46.67% were ASA 1 and 53.33 ASA 2. The data suggests that both the groups were comparable considering ASA grading of the patients.

Table-6: Hemodynamic parameters- Heart Rate

HEART RATE	GROUP D (N=30)		GROUP C (N=30)		t	p
	Mean	sd	Mean	sd		
Base line	78.03	9.33	76.66	1.10	**0.51**	**0.60**
5 minutes	76.06	8.83	75.73	1.13	**0.12**	**0.89**
15 minutes	75.80	9.14	74.40	1.23	**0.50**	**0.61**
30 minutes	74.70	1.01	75.33	1.18	**-0.22**	**0.82**
45 minutes	74.20	1.13	74.93	1.11	**-0.25**	**0.80**
60 minutes	73.40	1.14	75.06	1.13	**-0.56**	**0.57**
75 minutes	73.93	11.42	74.60	12.23	**-0.21**	**0.82**
90 minutes	74.60	1.02	74.33	1.16	**0.09**	**0.92**
105 minutes	74.80	9.67	74.53	11.48	**0.09**	**0.92**
120 minutes	74.80	9.20	74.86	11.54	**-0.25**	**0.98**
135 minutes	74.93	9.71	74.80	11.15	**0.04**	**0.96**
150 minutes	75.50	9.52	75.90	10.40	**-0.54**	**0.58**
165 minutes	74.13	9.74	75.86	10.45	**-0.58**	**0.50**
180 minutes	74.26	10.05	75.80	10.56	**-0.52**	**0.55**

Graph-5: Hemodynamic Parameters - Heart Rate

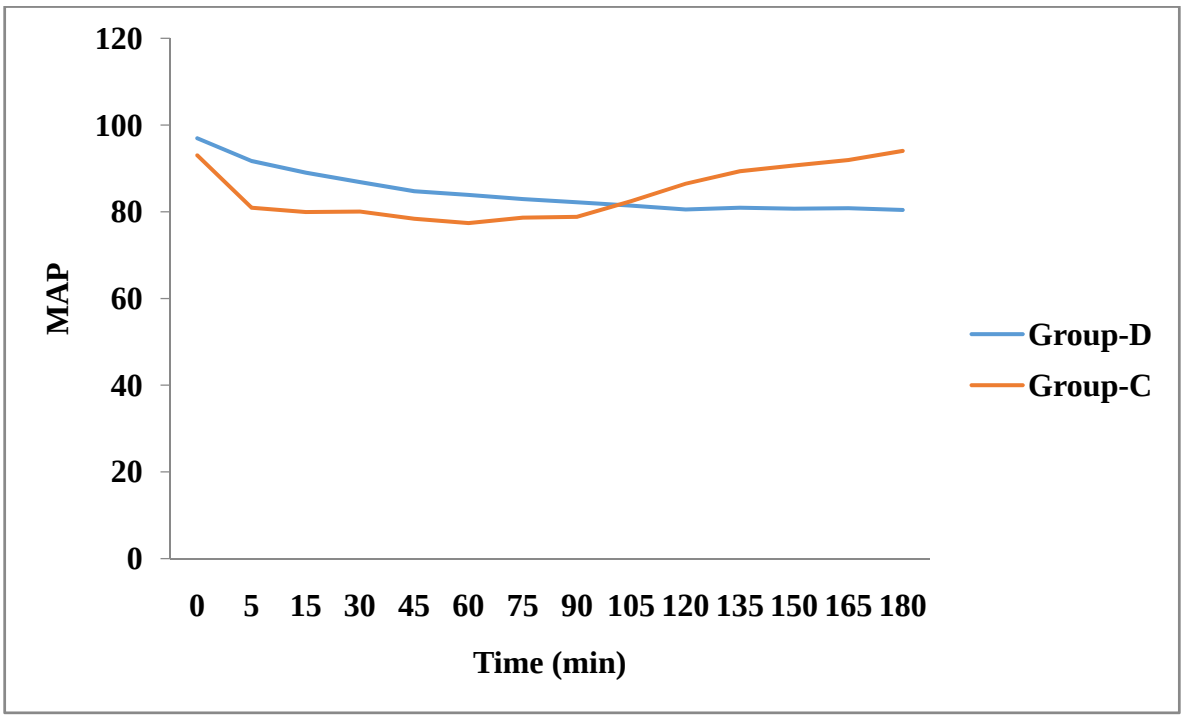


The mean baseline heart rate was 78.03±9.33 in group D and 76.66±1.10 in group C. In group D patients at 45, 60 and 75 minutes there was a gradual fall in heart rate but with no further significant biphasic changes throughout surgery when compared to group C . The mean HR from 105 to 180 minutes in group C is observed to have a steeper rise towards the latter half of surgery.

Table 7. Hemodynamic Parameters - Mean Arterial Pressure

MAP	GROUP D (N=30)		GROUP C (N=30)		t	p
	Mean	sd	Mean	sd		
Base line	96.96	6.86	93.03	8.73	1.93	0.05
5 minutes	91.73	9.42	80.93	1.31	3.65	0.001
15 minutes	89.03	7.58	79.96	1.07	3.76	0.001
30 minutes	86.86	8.04	80.06	1.11	2.71	0.009
45 minutes	84.73	8.87	78.40	8.83	2.77	0.008
60 minutes	83.90	8.23	77.40	7.26	3.24	0.002
75 minutes	82.93	7.87	78.66	9.02	1.95	0.05
90 minutes	82.20	7.51	78.83	9.07	1.56	0.12
105 minutes	81.43	7.31	82.46	11.26	-0.42	0.67
120 minutes	80.53	7.13	86.50	11.71	-2.38	0.20
135 minutes	80.96	6.48	89.36	11.02	-3.59	0.001
150 minutes	80.73	6.19	90.70	11.47	-4.18	0.001
165 minutes	80.83	6.76	91.96	10.96	-4.73	0.001
180 minutes	80.43	6.10	94.06	12.45	-5.38	0.001

Graph-6: Hemodynamic Parameters - Mean Arterial Pressure

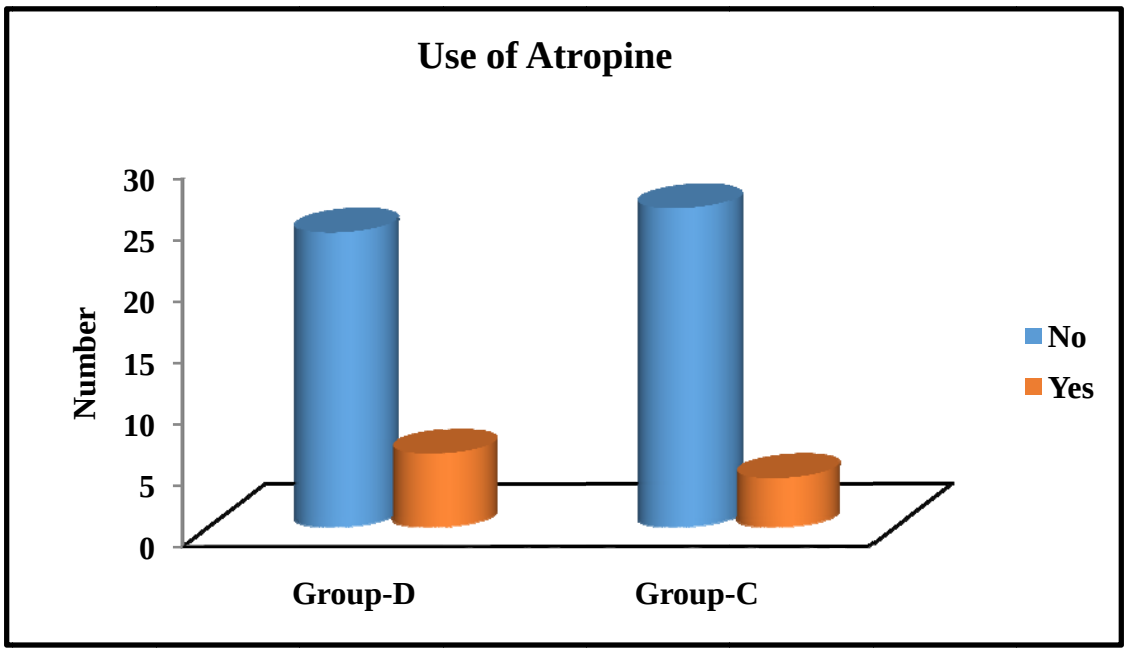


The baseline MAP was 96.96±6.86 in group D and 93.03±8.73 in group C, p value 0.05 suggesting that baseline MAP was comparable in both the study groups. A fall in MAP was observed with both groups following intrathecal block. The fall in MAP was steeper in group C up to 90 minutes following spinal anaesthesia, lowest reading was at 60 minutes - 77.40±7.26, and that in group D was 83.90±8.23, p=0.002 which makes the difference statistically significant. At 135 minutes the mean MAP of group D was 80.96±6.48and that in group C was 89.36±11.02 which indicates a steep rise in MAP in group C, p=0.001. From the above observations it is to be assumed that rise and fall in MAP is significantly relatively steeper in group C when compared with group D.

Table 8. Use of Atropine

Use of Atropine	Group D		Group C		Total	
	N	%	N	%	N	%
No	24	80.0	26	86.67	50	83.33
Yes	6	20.0	4	13.33	10	16.66
Total	30	100.0	30	100.0	60	100.0

Graph-7: Use of Atropine

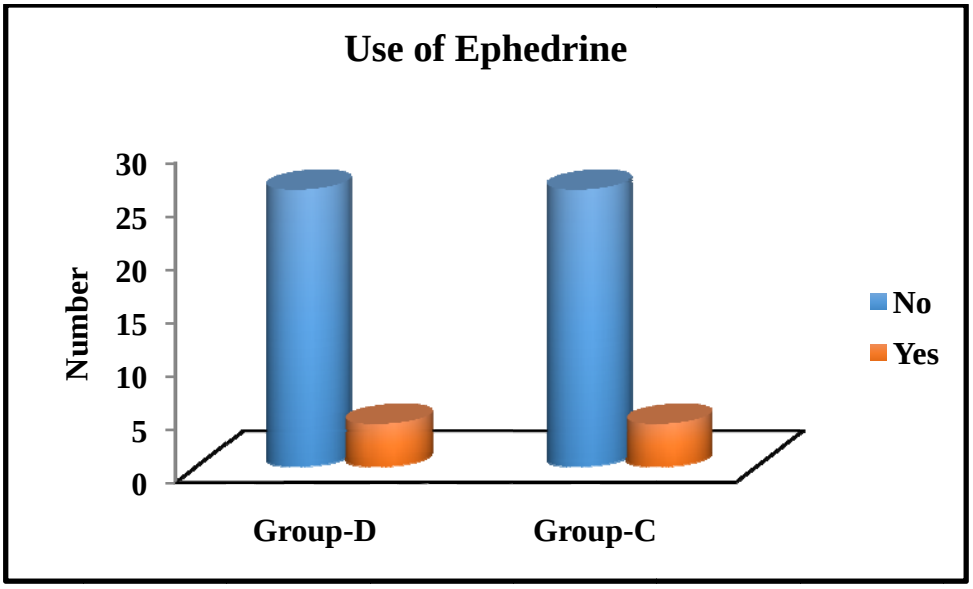


In group D 20% of the patients required Atropine following fall in heart rate, whereas in group C only 13.3% of the patients required Atropine which shows that use of Dexmedetomidine was associated with mild degrees of bradycardia in a minority but with no undue adverse effects.

Table 9. Use of Ephedrine

Use of Ephedrine	Group D		Group C		TOTAL	
	N	%	N	%	N	%
N	26	86.67	26	86.67	52	86.66
Y	4	13.33	4	13.33	8	13.33
Total	30	100.0	30	100.0	60	100.0

Graph-8: Use of Ephedrine

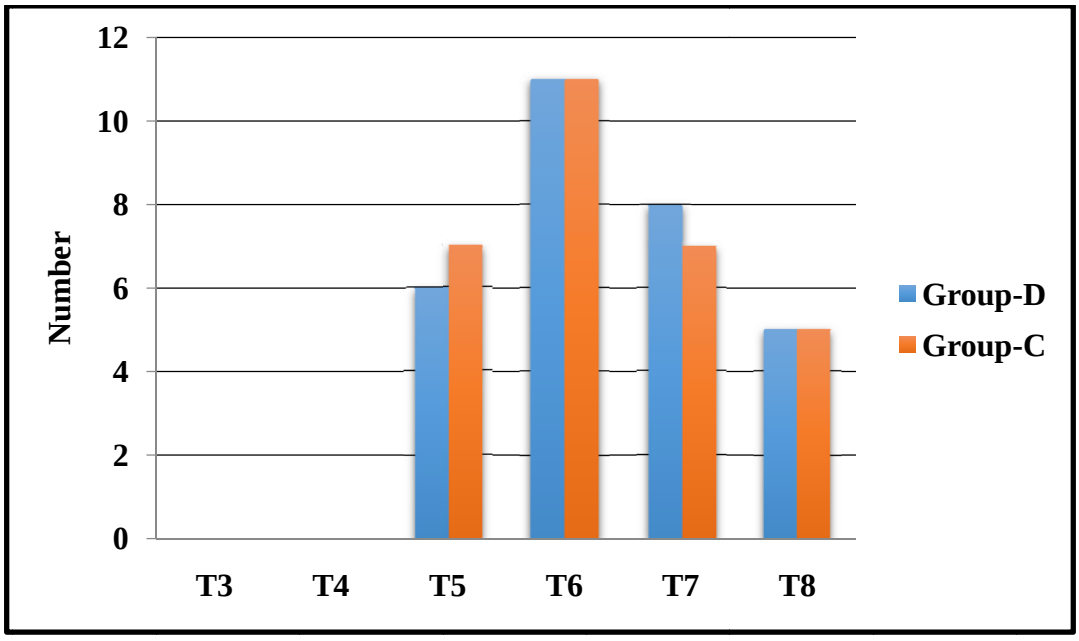


The above observations indicative of comparable levels of need for Ephedrine following fall in blood pressure in both group D and C.

Table 10. Level of Sensory Block

Highest block level	Group D		Group C		Total	
	N	%	N	%	N	%
T5	06	20.00	07	23.33	13	21.66
T6	11	36.67	11	36.67	22	36.67
T7	08	26.66	07	23.33	15	25.00
T8	05	16.67	05	16.67	10	16.67
Total	30	100	30	100	60	100

Graph-9: Level of sensory block



In both the groups the highest level of block was at the level of T5. In both the groups majority of the patients attained a highest level of block at T6.

Table-11: Duration of Sensory Block

Duration of sensory block	Group D		GROUP C		TOTAL	
	N	%	N	%	N	%
<60	0	0	0	0	0	0
61-120	10	33.33	30	100	40	66.67
121-180	19	63.34	0	0	19	31.67
181-240	1	3.33	0	0	1	1.66
Total	30	100.0	30	100.0	60	100.0

Graph-10: Duration of Sensory Block

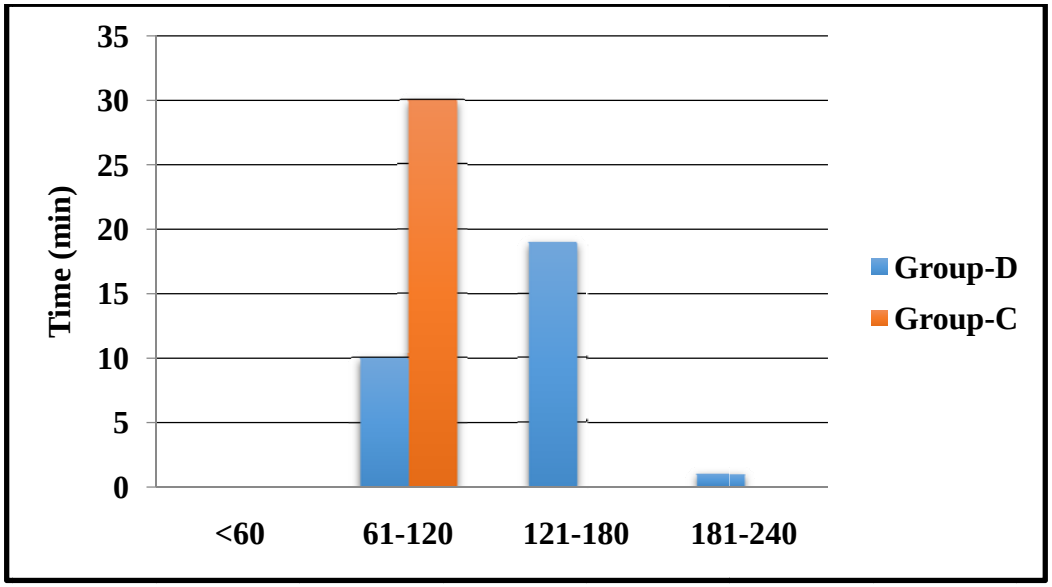


Table 12. Time for two dermatome regression of sensory blockade

CATEGORY	N	Duration of sensory block in minutes		t	p
		Mean	sd		
Group D	30	138.33	2.10	15.35	0.001
Group C	30	76.00	7.23		

In group D 63.34% of patients had sensory block lasting for 121-180 minutes, 33.33% had for 61-120 minutes, and for 3.33% the sensory block lasted for up to 180 minutes. Whereas in group C, all the patients had sensory block lasting for not more than 120 minutes before the initiation of dermatome level regression. From the observations of the mean values, sensory block duration was significantly higher in group D (138.33) than in group C (76), p=0.001.

Table-13: Duration of Motor Block

Duration of motor block (in	GROUP D		GROUP C		TOTAL	
	N	%	N	%	N	%
61-120	0	0	11	36.67	11	18.33
121-180	21	70.00	19	63.33	40	66.67
181-240	9	30.00	0	0	9	15.00
Total	30	100.0	30	100.0	60	100.0

Graph-11: Duration of motor nerve block

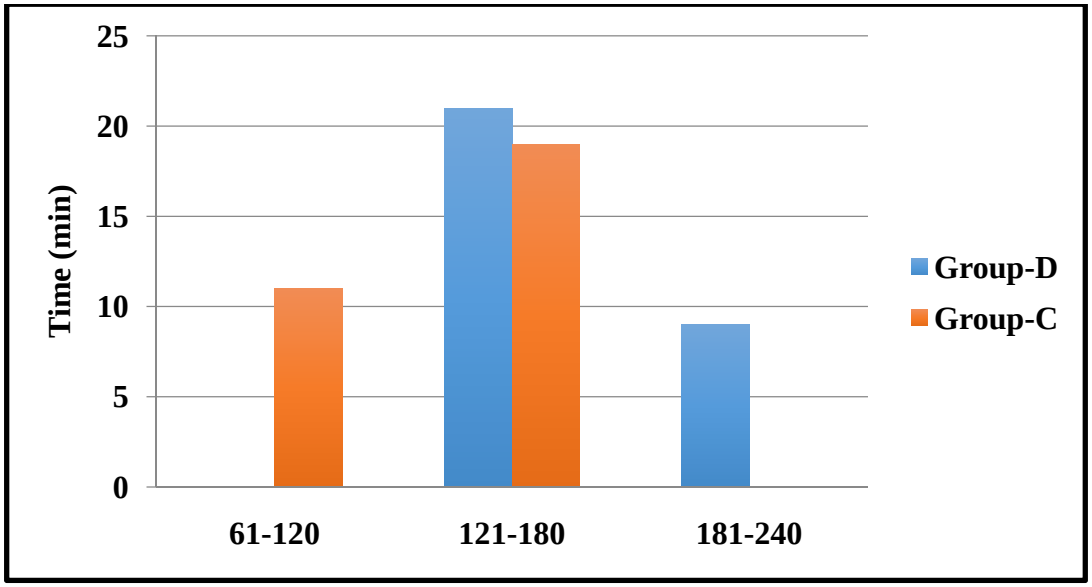


Table-14: Time for return to Modified Bromage Scale to 0

CATEGORY	N	Duration of motor block in minutes		t	p
		Mean	sd		
Group D	30	179	1.08	9.23	0.001
Group C	30	137.67	2.22		

In group D 70% of the patients were noted to have a motor block duration of 121-180 minutes and in 30% it lasted for 181-240 minutes. In group C 63.33% of the patients had motor block lasting for 121-180 minutes and for 36.67 the block lasted not more than 180 minutes. From the observations of the mean values, motor block in group D (179) was significantly higher than that in group C (137.67), p= 0.001.

Table-15: Time at request for first post operative analgesia

Time (min)	Group-D		Group-C		Total	
	N	%	N	%	N	%
60-120	0	0	4	13.33	4	6.67
121-180	1	3.33	21	70.00	22	36.67
181-240	15	50.00	5	16.67	20	33.33
241-300	12	40.00	0	0	12	20.00
>301	2	6.67	0	0	2	3.33
Total	30	100	30	100	60	100

Graph-12: Time at request for first post operative analgesia

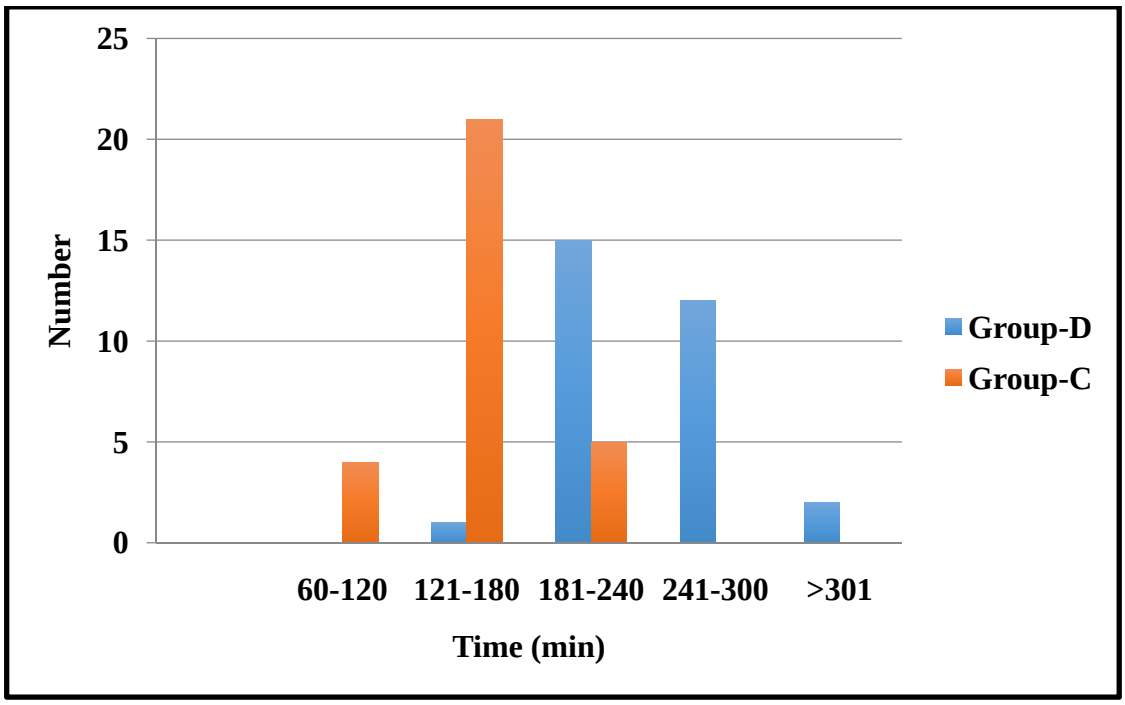


Table-16: Comparison of mean values of time to rescue analgesia

CATEGORY	N	Time at request for first post-operative		t	p
		Mean	sd		
Group D	30	241.67	3.47	10.94	0.001
Group C	30	155.00	2.59		

The time of request for first analgesia in the postoperative period in 50% of the group D patients was between 181-240 minutes and for 40% between 241-300 minutes, whereas in group C 70% of the patient required rescue analgesia between 121-180 minutes and 16.67% between 181-240 minutes. All the group C patients required rescue analgesia in less than 240 minutes while 6.67% of the patients in group D requested for rescue

analgesia only after 300 minutes. The observations show that time of request for rescue analgesia in the postoperative period was significantly extended in group D (241.67±3.47) when compared to group C (155±2.59), p=0.001.

Table-17: Ramsay Sedation Score

Sedation score	Group D		Group C		Total	
	N	%	N	%	N	%
2	4	13.33	30	100	34	56.67
3	26	86.67	0	0	26	43.33
4	0	0	0	0	0	0
Total	30	100	30	100	60	100

Table-18: Comparison of sedation scores

Sedation score	Group D		Group C		Total	
	N	%	N	%	N	%
<4	30	100	30	100	60	100
>4	0	0	0	0	0	0
Total	**30**	**100**	**30**	**100**	**60**	**100**

86.67% of the patients in group D had a Ramsay sedation score of 3 and 13.33% had a score of 2, whereas all the patients in group C had Ramsay sedation score of 2 only, this shows that sedation score of the patients in group D was significantly high.

DISCUSSION

This is a quasi interventional trial completed in a period of one year in the Department of Anaesthesiology, Sree Mookambika Institute of Medical Sciences, Padanilam, Kulasekharam, Kanyakumari District. A total of 60 patients undergoing lower abdominal and lower limb surgeries under bupivacaine spinal anaesthesia were randomly divided into two groups on an alternate basis, Group D - the study group (n=30) and Group C – the control group (n=30). For patients in Group D Inj. Dexmedetomidine 0.5mcg/kg diluted in 10ml of sterile water was given as premedication intravenously over 10mins half an hour before surgery, whereas patients in Group C received 10ml of normal saline intravenously instead of Dexmedetomidine over 10mins.

In this study male subjects formed the majority in both the groups, 66.7% in Group D were males and 33.3% females whereas in Group C 76.76% were males and 23.33% females. In both the groups majority of the patients belonged to age group between 31-50 years suggesting that both the study groups were comparable with regard to the demographic variables. The mean age was 39.93 in group D and 38.46 in group C. The mean height in group D was 159.60±5.39 and that in group C 162.60±6.68. The mean weight was 59.93±5.92 in group D and 67.23±4.05 in group C. In group D 50% of the patients were ASA 1 and 50% ASA 2, whereas in group C 46.67% were ASA 1 and 53.33 ASA 2. Thus both the groups were comparable with regard to height, weight and ASA grade.

Earlier studies[38,39] have showed that bradycardia due to Dexmedetomidine as a premedication is long lasting. This reflects the decreased sympathetic outflow and circulating levels of catecholamines caused by administration of Dexmedetomidine. In this study, the mean baseline heart rate was 78.03±9.33 in group D and 76.66±1.10 in group C. In group D patients at 45, 60 and 75 minutes there was a gradual fall in heart rate but with no further significant biphasic changes throughout surgery when compared to group C. The mean HR from 105 to 180 minutes in group C is observed to have a steeper rise towards the latter half of surgery.

Rapid infusion of lower concentration or bolus administration of larger concentration of Dexmedetomidine is known to produce rapid rise in blood pressure and fall in heart rate as long as the central sympatholytic effect remains, causing moderate decreases in both mean arterial pressure and heart rate from the baseline readings. But no biphasic change or significant cardiovascular variation was noted in the study probably reflecting the effect of sympathetic blockade associated with spinal anaesthesia, slow rate of administration, and adequate prehydration. [40] In a study 48 patients belonging to ASA I/II/III posted for TURP/TURT/TVT were randomly divided equally into two groups receiving isobaric bupivacaine (12.5 mg) spinal anaesthesia. Patients in group D were given a loading dose of 1mcg/kg Dexmedetomidine intravenously over 10 min and 0.5mcg/kg/hr for maintenance of anaesthesia; patients in group C (the control group) received normal saline instead. It was concluded that iv

Dexmedetomidine prolonged the sensory and motor blocks of bupivacaine spinal analgesia with excellent sedation and hemodynamic stability. Adverse effects were eluded by slow infusion of Dexmedetomidine. All patients had arousable deep levels of sedation without ventilatory depression, enabling their cooperation and better operating conditions for the surgeons. Decrease in the heart rate was more profound but insignificant in patients who received intravenous Dexmedetomidine compared to those who received normal saline. [26]In a near similar study the lowest heart rate noted was 61.7±6.2 in Dexmedetomidine group and 63.1±7.1 in normal saline group, which was statistically comparable. The incidence of bradycardia requiring management with atropine was relatively higher in group D (23.3%) than in group P (20.0%); but this difference was statistically not significant (p=0.754).

Similarly in a study done by Hall JE et al[41] to assess the safety and efficacy of two small dose infusions of Dexmedetomidine by evaluating sedation, analgesia and cardio respiratory function in seven healthy young volunteers who participated on three different occasions with random allocation to drug or placebo. Baseline parameters were recorded, and psychometric tests were carried out which included visual analog scale [VAS] for sedation; observer's assessment of alertness/sedation scale; digit symbol substitution test; and memory. After a 10 minute initial dose of normal saline or 6mcg/kg/hr Dexmedetomidine, volunteers received IV infusions of normal saline, or 0.2 or 0.6 mcg/kg/hr Dexmedetomidine over

50 minutes. The Dexmedetomidine infusions provided similar, significant sedation (30%-60%), memory impairment (approximately 50%), and impairment of psychomotor performance (28%- 41%). Hemodynamic status, peripheral oxygen saturation, $ETCO_2$, and respiratory rate were well preserved throughout. Analgesic requirement was reduced following Dexmedetomidine infusion. Small dose of Dexmedetomidine produced sedation, analgesia, and memory and cognitive impairment; and infusions produced arousable sedation, mild analgesia, and memory impairment without cardio respiratory compromise.

[4]Another study reported an incidence of only two patients requiring atropine for bradycardia in Dexmedetomidine group and one in saline group (n=25).

In the present study the baseline MAP was 96.96±6.86 in group D and 93.03±8.73 in group C, p value 0.05 suggesting that baseline MAP was comparable in both the study groups. A fall in MAP was observed with both groups following intrathecal block. The fall in MAP was steeper in group C up to 90 minutes following spinal anaesthesia, lowest reading was at 60 minutes - 77.40±7.26, and that in group D was 83.90±8.23, p=0.002 which makes the difference statistically significant. At 135 minutes the mean MAP of group D was 80.96±6.48and that in group C was 89.36±11.02 which indicates a steep rise in MAP in group C, p=0.001. From the above observations it is to be assumed that both rise and fall in MAP is significantly relatively steeper in group C when compared with group D.

[42]In another study previously done there was fall in mean arterial pressure in both groups but was not clinically significant. And yet another study[4] noted the lowest MAP in Dexmedetomidine group as 79.9±6.8 and in Saline group 83.2±7.2, which was statistically comparable. These results reflect the findings in our present study. A biphasic cardiovascular response has been demonstrated following administration of Dexmedetomidine; there was a transient increase in MAP and a reflex decrease in HR, due to direct effects of α_{2B}-adrenoceptor stimulation of vascular smooth muscle, especially in the young healthy patients. This response can be reduced by a slow infusion of the drug over 10 min; but transient enhancement of mean arterial BP and the fall in HR over the first 10 min has been demonstrated even at slower infusion rates. The transient increase in BP lasts for 5 to 10 min, followed by fall in BP of 10-20% below the baseline value and by stable HR below the baseline values. These effects are probably caused by an inhibition of central sympathetic outflow overriding the direct action of Dexmedetomidine on the vasculature Postsynaptic stimulation of central α_2-AR's cause sympatholytic effect leading to hypotension and bradycardia, an effect judiciously produced to attenuate the stress response of the ongoing procedure [43,44]. Dexmedetomidine induced hypotension and bradycardia are readily reversed by ephedrine and atropine respectively.[42]

In our study the need for ephedrine following fall in blood pressure had comparable levels in both the groups. [26]In a study 2 out of 25 patients in Dexmedetomidine group and 4 out of 25 patients in Normal Saline group

developed hypotension. Mahmoud et al, in their study observed the incidence of hypotension comparable in both groups.

In our study, peripheral oxygen saturation was maintained stable in both the groups at all time intervals. In the study conducted by Kaya FN et al[4] they observed no ventilatory depression in any of the patients and the respiratory parameters (rate, oxygen saturation, and $EtCO_2$) remained stable and within normal limits at all stages throughout the procedure. Another study[40] showed higher oxygen saturation (> 95%) in all patients in the two groups in the perioperative period.

In our study 86.67% of the patients in group D had a Ramsay sedation score of 3 and 13.33% had a score of 2, whereas all the patients in group C had Ramsay sedation score of 2 only, this shows that sedation score of the patients in group D was significantly high. It is noteworthy that even with excessive sedation (score of 3), the oxygen saturation remained comparable to the control group which is suggestive of Dexmedetomidine producing sedation without ventilatory depression, making it a near ideal sedative agent, the difference from other sedative agents being arousable sedation with better patient cooperation. Kaya FN et al[4] in their study demonstrated excessive sedation in 2 out of 25 patients belonging to Dexmedetomidine group and 5 out of 25 in midazolam group and no incidence in the saline group.

The hypnotic and supraspinal analgesic action of Dexmedetomidine are regulated by the hyperpolarisation of noradrenergic neurons, leading to stimulation of K^+ channel, Ca^{2+} inhibition, inhibition of adenylcyclase which subdue neuronal firing in the locus ceruleus along with inhibition of norepinephrine release and its effect on the descending medullo-spinal noradrenergic pathway, secondary to activation of central α_2-AR s. This in turn triggers neurotransmitters that reduce the histamine secretion providing hypnosis similar to normal sleep, (with no ventilatory depression), making Dexmedetomidine a near ideal sedative agent[81]. Subdued activity in the descending noradrenergic pathway, which mediates nociceptive neurotransmission, terminates the propagation of pain signals leading to analgesia.[45]

In our study in both the groups the highest level of block was at the level of T5. In both the groups majority of the patients attained a highest level of block at T6. Kaya FN et al in their study[4] recorded the highest level of sensory block significantly higher ($p<0.001$) in Dexmedetomidine group of patients (T4.6±0.6) than in saline group of patients (T6.4±0.8).

In the present study in group D 63.34% of patients had sensory block lasting for 121-180 minutes, 33.33% had for 61-120 minutes, and for 3.33% the sensory block lasted for more than 180 minutes. Whereas in group C, all the patients had sensory block lasting for not more than 120 minutes before the initiation of dermatome level regression. From the observations of the mean values, sensory block duration was significantly higher in group D

(138.33) than in group C (76), p=0.001. These results are invariable with the results obtained in a study conducted by Kaya FN et al[4], a double blinded randomized placebo controlled trial study in 2010, on the effects of intravenous Dexmedetomidine comparing it with intravenous midazolam on spinal anaesthesia, analgesia and sedation in patients posted for transurethral resection of the prostate (TURP) on 75 patients belonging to American Society of Anaesthesiologists' (ASA) I and II - 25 patients in each group. Patients were given Dexmedetomidine 0.5 μg/kg, midazolam 0.05μg/kg or saline intravenously before intrathecal block with 15mg of 0.5% bupivacaine. Sensory block was higher with Dexmedetomidine group (T4.6±0.6) than with midazolam group (T6.4±0.9; P<0.001) or saline group (T6.4±0.8; P<0.001).Time for sensory two dermatomes regression was 145± 26 min in the Dexmedetomidine group, and lasted longer (p<0.001) than that in the midazolam group (106±39 min) or the saline group (97±27). Duration of motor block was alike in all the three groups. Dexmedetomidine seemed to increase the first time request for postoperative analgesia (p<0.01) compared to midazolam and saline group, and decreased the analgesic requirements (p<0.05). The maximum Ramsay sedation score was higher in the Dexmedetomidine and midazolam groups than in the saline group (p<0.001). It was concluded that, intravenous Dexmedetomidine prolonged spinal bupivacaine sensory blockade, but not midazolam, and it also provided sedation and added analgesia.

In group D 70% of the patients were noted to have motor block duration of 121-180 minutes and in 30% it lasted for 181-240 minutes. In group C 63.33% of the patients had motor block lasting for 121-180 minutes and for 36.67 the block lasted not more than 180 minutes. From the observations of the mean values, motor block in group D (179) was significantly higher than that in group C (137.67), p= 0.001. These results are invariable with results obtained in a study[57] conducted on 50 ASA I/II patients posted for infra umbilical surgeries. Patients were randomly divided equally into two groups receiving isobaric bupivacaine (12.5 mg) spinal anaesthesia. Patients in group D were given a loading dose of 0.5mcg/kg Dexmedetomidine intravenously over 10 min and patients in group C (the control group) received normal saline instead. The motor block duration was significantly prolonged in group D than in the control group concluding that iv Dexmedetomidine prolonged the sensory and motor blocks of bupivacaine spinal analgesia with excellent sedation and hemodynamic stability.

Another study[2] demonstrated that combination of 12 mg of bupivacaine with a low dose (3 mcg) of Dexmedetomidine or 30 mcg of clonidine administered intrathecal significantly reduced the onset of motor block and extended both motor and sensory block when compared with bupivacaine alone. In this prospective, double blind study, 60 patients posted for TURP or transurethral resection of bladder tumor under spinal anaesthesia were randomly divided in to three groups to compare the onset,

duration and level of sensory and motor block, the hemodynamic variation and level of sedation following intrathecal bupivacaine with either Dexmedetomidine or clonidine as adjuvants. Group B were given 12 mg of hyperbaric bupivacaine, group D 12 mg of bupivacaine with 3 mcg of Dexmedetomidine and group C 12 mg of bupivacaine with 30 mcg of clonidine as adjuvants. Patients in groups D and C the onset of motor block was significantly shorter and sensory and motor regression times significantly longer in group B. In group D the mean time of sensory regression to the S1 level was 303 +/- 75 min, 272 +/- 38 min in group C and 190 +/- 48 min in group B ($p < 0.001$). The motor block regression to Bromage 0 was 250 +/- 76 min in group D, 216 +/- 35 min in group C and 163 +/- 47 min in group B ($p < 0.001$). The onset and regression times were not significantly different between groups D and C. The MAP, HR and sedation levels were similar in the all the three groups intra and postoperatively. It was concluded that 3 mcg Dexmedetomidine or 30 mcg clonidine as an adjuvant to intrathecal bupivacaine, produces a similar prolonged motor and sensory block duration preserved hemodynamic stability and lack of sedation.

Considering the present as well as the earlier studies it can be concluded that the effect of Dexmedetomidine on duration of spinal and motor blockade is independent on route of administration of Dexmedetomidine. Nevertheless, an intravenous route ensures a safer effective adjunct to subarachnoid block. The drawbacks of

Dexmedetomidine as an adjuvant for intrathecal block may include enhanced duration of motor block not suitable for ambulatory procedures.

In our study the time of request for first analgesia in the postoperative period in 50% of the group D patients was between 181-240 minutes and for 40% between 241-300 minutes, whereas in group C 70% of the patient required rescue analgesia between 121-180 minutes and 16.67% between 181-240 minutes. All the group C patients required rescue analgesia in less than 240 minutes while 6.67% of the patients in group D requested for rescue analgesia only after 300 minutes. The observations show that time of request for rescue analgesia in the postoperative period was significantly extended in group D (241.67±3.47) when compared to group C (155±2.59), p=0.001. These findings are invariable with the results of a similar study[26] carried out to establish that iv Dexmedetomidine and not midazolam prolongs bupivacaine spinal anesthesia. The researchers noted that time of first request for rescue analgesia was 216±43 minutes in Dexmedetomidine group of patients, and significantly sooner in the saline group 122±34 minutes ($p<0.001$).

α_2-receptor agonists demonstrate analgesic effect when administered via the intrathecal or epidural route. The primary site of action is thought to be at the spinal cord. Narcotic sparing is observed with systemic use of Dexmedetomidine[24]. Dexmedetomidine restrain the release of substance P from the dorsal horn of the spinal cord, which is also responsible for primary analgesic effects.[22]

A study[48] demonstrated that Dexmedetomidine has an inhibitory action on the locus ceruleus (A6 group) present at the brain stem. The prolongation of spinal anaesthesia is indicative of the supraspinal action of Dexmedetomidine when given intravenously. The noradrenergic innervation of the spinal cord emerges from the noradrenergic nuclei present in the brain stem which also includes the locus ceruleus, the A5, and the A7 noradrenergic nuclei. Neurons in the locus ceruleus are linked to the noradrenergic nuclei. The noradrenergic axon terminals reach lamina VII and VIII of the ventral horns of the spinal cord. The activity of the noradrenergic neurons is reduced by agonists acting at α_2-AR on the locus ceruleus. Therefore, inhibition of the locus ceruleus activates the noradrenergic nuclei and produce descending inhibitory effect on nociception.[22]

The hypnotic and supraspinal analgesic action of Dexmedetomidine are regulated by the hyperpolarisation of noradrenergic neurons, leading to stimulation of K^+ channel, Ca^{2+} inhibition, inhibition of adenylcyclase which subdue neuronal firing in the locus ceruleus along with inhibition of norepinephrine release and its effect on the descending medullo-spinal noradrenergic pathway, secondary to activation of central α_2-AR s. This in turn triggers neurotransmitters that reduce the histamine secretion providing hypnosis similar to normal sleep, (with no ventilatory depression), making Dexmedetomidine a near ideal sedative agent. Subdued activity in the descending noradrenergic pathway, which mediates nociceptive

neurotransmission, terminates the propagation of pain signals leading to analgesia.[26]

To summarize, in our study, the use of intravenous Dexmedetomidine as premedication prolonged the duration of sensory and motor block while maintaining a stable hemodynamic profile and providing adequate arousable sedation. For the same, intravenous Dexmedetomidine seem to offer a clinical advantage as an adjunct to bupivacaine spinal anaesthesia, where a longer duration of anaesthesia is called for without the use of higher dose of local anaesthetic and to reduce the analgesic requirement.

Dexmedetomidine, owing to its physiochemical properties of hemodynamic stability, is safe to be used in patients with limited functional reserve, and thereby omits the requirement for excessive fluids.

The α_2-AR acts through the intrinsic sleep promoting pathways so as to produce their sedative effects. It provides a unique sedative quality described as "Clinically sedated yet arousable". Despite sound levels of sedation with the administration of Dexmedetomidine there was no respiratory depression providing a wide safety margin.[30]

A limitation of this study is that the time of first request for rescue analgesia was used as the primary index for post operative analgesia instead of the standard VAS scores. This study also shows the relative shortcomings of the use of Dexmedetomidine in view of motor blockade prolongation which is undesirable postoperatively resulting in patient anxiety which is of particular importance in daycare surgeries.

CONCLUSION

The present study showed that intravenous Dexmedetomidine as premedication for Bupivacaine spinal anaesthesia prolonged the duration of sensory and motor blockade and the time of request for rescue analgesia. It also provided arousable sedation without respiratory depression and maintained a stable hemodynamic profile throughout the perioperative period.

SUMMARY

Spinal anaesthesia also called subarachnoid/intrathecal block is a popular technique carried out for a variety of surgical procedures involving the lower abdominal and lower limb surgeries. Dexmedetomidine is a highly potent novel α_2-adrenoceptor agonist with a higher $\boldsymbol{\alpha_2/\alpha_1}$selectivity of 1000:1. The aim of the present study is to assess the effects of intravenous Dexmedetomidine as premedication on the onset, level and duration of sensory and motor blockade, analgesia and sedation in patients undergoing lower abdominal and lower limb surgeries under Bupivacaine (hyperbaric, 0.5%, 3mL) spinal anaesthesia.

This is a quasi interventional trial completed in a period of one year in the Department of Anaesthesiology, Sree Mookambika Institute of Medical Sciences, Padanilam, Kulasekharam, Kanyakumari District. A total of 60 patients undergoing lower abdominal and lower limb surgeries under bupivacaine spinal anaesthesia were randomly divided into two groups on an alternate basis, Group D - the study group (n=30) and Group C – the control group (n=30). In Group D Inj. Dexmedetomidine 0.5mcg/kg diluted in 10ml of sterile water was given as premedication intravenously over 10mins half an hour before surgery, whereas patients in Group C received 10ml of normal saline intravenously instead of Dexmedetomidine over 10mins.

In the present study 33.3% in Group D were females and 66.7%

males whereas in Group C 23.33% females and 76.76% were males. The mean age in group D was 39.93 and 38.46 in group C and the mean weight was 59.93±5.92 in group D and 67.23±4.05 in group C. Both the groups were comparable regarding sex, age, height and weight. The biphasic change in heart rate and mean arterial pressure were insignificant. Arterial oxygen saturation did not fall below 97% in both groups throughout the study. The need for injection Atropine and Ephedrine was comparable in both groups. The sensory block duration was significantly higher in group D (138.33) than in group C (76), p=0.001, and the motor block in group D (179) was significantly higher as well than that in group C (137.67), p= 0.001. The time of request for rescue analgesia in the postoperative period was significantly extended in group D (241.67±3.47) when compared to group C (155±2.59), p=0.001. The Ramsay sedation score of the patients in group D was significantly high - 86.67% of the patients had a sedation score of 3 whereas all the patients in group C had Ramsay sedation score of 2 only.

In short, it may be concluded that intravenous Dexmedetomidine as premedication for Bupivacaine spinal anaesthesia prolonged the duration of sensory and motor blockade and the time of request for rescue analgesia. It also provided arousable sedation without respiratory depression and maintained a stable hemodynamic profile throughout the perioperative period.

BIBLIOGRAPHY

1. Ankorn C, Casey WF. Spinal Anaesthesia - a practical guide 2000 ; (12):21-34.
2. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, AlameddineMM, Al-Yaman R, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. *Acta Anaesthesiol Scand.* 2006; 50(2):222-7.
3. Panzer O, Moitra V, Sladen RN. Pharmacology of Sedative-Analgesic Agents: Dexmedetomidine, Remifentanil,Ketamine, Volatile Anesthetics, and the Role of Peripheral μ Antagonists.*Crit CareClin*2009; 25(3):451-69, vii.
4. Kaya FN, YavascaogluB,Turker G, Yildirim A, Gurbet A, Mogol EB, et al. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. *Can J Anaesth*2010; 57(1):39-45.
5. Corning, JL (1885). "Spinal anaesthesia and local medication of the cord". New York Medical Journal 42: 483–5.
6. Turnbull DK, Shepherd DB. Post dural puncture headache: Pathogenesis, prevention and treatment. *Br J Anaesth* 2003; 91(5):718-29.
7. Brown DL. Spinal block in Atlas of Regional Anesthesia. 2nd ed., Philadelphia: WB SaundersCompany;1999

8. dos Reis A Jr. Eulogy to August Karl Gustav Bier on the 100th anniversary of intravenous regional block and the 110thanniversary of the spinal block. *Rev Bras Anestesiol*2008; 58(4):409-24.

9. Atkinson RS, Rushman GB, Davies NJH. Spinal analgesia: Intradural and Extradural. In: *Lee's Synopsis of Anesthesia,*11th ed., UK: ELBS; 1993.p.691-745.

10. Fettes PDW, Jansson JR, Wildsmith JAW. Failed spinal anaesthesia: Mechanisms, management and prevention. *Br J Anaesth* 2009; 102(6):739-48.

11. Perlas A, Chan VW. Neuraxial anesthesia and multiple sclerosis. *CanJ Anaesth* 2005; 52(5):454-8.

12. Williams PL, Warwick R, Dyson M, Bannister LH. Gray's anatomy. 37thEd. NewYork: Chruchill Livingstone;1989

13. Healy TEJ, Cohen PJ. *Wylie and Churchill-Davidson's A Practice of Anaesthesia* 6th ed., London: Hodder Arnol Publication; 1995.

14. Pinnock C, Lin T, Smith T. Fundamentals of Anaesthesia. 2nded., London: Greenwich Medical Media Ltd.; 2003.

15. Greene NM. Distribution of local anesthetic solution within the subarachnoid space. *Anaesth Analg*1985; 64:715-30.

16. Raymond Fink BR. Mechanisms of differential axial blockade in epidural and subarachnoid anesthesia. Anaesthesiology 1989; 70:815-58.

17. Langer SZ. Presynaptic regulation of the release of catecholamines. Pharmacology Reviews 1980; 32:337-62.

18. Scheinin M, Schwinn D. The locus coeruleus: site of hypnotic actions of α_2-adrenoceptor agonists *Anesthesiology*1992; 76:873-5.

19. De Noyer M, Laveleye F, Vauquelin G, Gobert J, Wulfert E, Mivazerol.A novel compound with high binding specificity for α_2-adrenergic receptors: binding studies on different human and rat membrane. *NeurochemInt*1994; 24(3):221-9.

20. Dyck JB, Shafer SL. Dexmedetomidine pharmacokinetics and pharmacodynamics. Anaesthetic Pharmacology Review 1993; 1:238-45.

21. Ralph Getler, Clieghton H Brown, Mitchel H, Silvius N. Dexmedetomidine: a novel sedative analgesic agent. Baylor University Medical Centre Proceedings. 2001;14(1).

22. Gertler R, Cleighton Brown H, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc (BaylUniv Med Cent) 2001; 14(1):13-21.

23. Hossman V, Maling TJB, Hamilton CA, Reid JL, Dollery CT. Sedative and cardiovascular effects of clonidine and nitrazepam. ClinPharmacolTher1980; 28:167-76.

24. Martin E, Ramsay G, Mantz J, Sum-Ping ST. The role of the α_2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. J Intensive Care Med. 2003; 18(1):29-41.

25. Drummond JC. Dexmedetomidine, a α_2-adrenergic agonist decreases

cerebral blood flow in the isoflurane anesthetized dog. AnesthAnalg1990; 70:624-30.

26. Grewal A. Dexmedetomidine: New avenues. J Anaesthesiol ClinPharmacol2011; 27:297-302.
27. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, Murshidi MM, Ammari BA, AwwadZM, et al. Effect of dexmedetomidine added to spinal bupivacaine for urological procedures. Saudi Med J 2009; 30(3):365-70.
28. Eid HEA, Shafie MA, Youssef H. Dose-Related Prolongation of Hyperbaric Bupivacaine Spinal Anesthesia by Dexmedetomidine. Ain Shams Journal of Anesthesiology 2011; 4(2):83-95.
29. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperativeinfusion of dexmedetomidinereducesperioperative analgesic requirements. CanJ Anaesth. 2006; 53(7):646-52.
30. Hayashi Y, Sumikawa K, Maze M, Yamatodani A, Kamibayashi T, Kuro M, et al. Dexmedetomidine prevents epinephrine-induced arrhythmiasthrough stimulation of central α_2-adrenoceptors in halothane anesthetized dogs. Anesthesiology 1991; 75:113-7.
31. Ooi R, Pattison J, FeldmanSA.The effects ofintravenous Clonidine on ventilation.Anaesthesia 1991; 46:632-3.
32. Belleville JP, Ward DS,Bloor BC, Maze M.EffectsofintravenousDexmedetomidinein humans. Anesthesiology 1992; 77:1125-33.

33. Smyth DD, Umemura S, Pettinger WA. α_2-adrenoceptor antagonism of vasopressin-induced changes insodium excretion.Am JPhysiol 1985; 248:F767-72.

34. Masal A, Satta G, Alagna S, Anania V, FrassettoGA,Rovasio PP, et al. Effect of clonidine onstress-induced cortisolrelease during surgery.PharmacolRes Comm 1985; 17:293-8.

35. Di Joseph JF, Taylor JA, Mir GN. α_2-receptors in the gastrointestinal system: a new therapeutic approach. Life Sci 1984; 35:1031-42.

36. Grant JA, Scrutton MC. Interaction ofselective α-adrenoceptoragonistsandantagonists withhuman and rabbitbloodplatelets.Br J Pharmacol1980; 71:121-34.

37. Salonen M, Reid K, Maze M. Synergistic interaction between α_2-adrenergic agonists and benzodiazepines in rats. Anesthesiology 1992; 76:1004-11.

38. Arain S R, Ebert TJ. The efficacy, side effects, and recovery characteristics of Dexmedetomidine versus propofolwhenused for intraoperativesedation. AnesthAnalg2002; 95:461-6.

39. Aantaa R, Jaakola Ml, Kallio A, Kanto J, Scheinin M, Vuorinen J.A comparison of Dexmedetomidine, and α_2-adrenoreceptor agonist, and midazolam as i.m premedication for minor gynaecological surgery. Br J Anaesth 1991; 67:402-9.

40. Al-Mustafa MM, Badran IZ, Abu-Ali HM, Al-Barazangi BA, Massad IM, AlGhanem SM. Intravenous dexmedetomidine prolongs

bupivacaine spinal analgesia. Middle East J Anesthesiol2009; 20(2):225-31.

41. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose Dexmedetomidine infusions. AnesthAnalg2000; 90(3):699-705.
42. Whizar-Lugo V, Gomez-Ramfrez I A, Cisneros-Corral R, Martfnez-Gallegos N. Intravenous Dexmedetomidine v/s Intravenous Clonidine to prolong Bupivacaine Spinal Anesthesia. A Double Blind Study.2007; 19(3):143-6.
43. Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY. Monitored AnesthesiaCare with Dexmedetomidine: A Prospective, Randomized, Double-Blind, Multicenter Trial. AnesthAnalg.2010; 110:47-56.
44. Ishii H, Kohno T, Yamakura T, Ikoma M, Baba H. Action of Dexmedetomidine on the substantia gelatinosa neurons of the rat spinal cord. Eur JNeurosci2008; 27:3182-90.
45. Ustun Y, Gunduz M, Erdogan O, Benlidayi ME. Dexmedetomidine versus midazolam in out patient third molar surgery. J Oral Maxillofac Surg 2006; 64:1353-8.
46. Nelson LE,You T,Maze M, FranksNP. Evidencethat themechanism of hypnoticactionindexmedetomidine andmuscimol-induced anesthesia converges onthe endogenous sleeppathway. Anesthesiology2001; 95:A1368.

47. Kanazi GE, AouadMT, Jabbour-Khoury SI,Al JazzarMD, AlameddineMM,Al-YamanR,et al.Effectoflow-dose dexmedetomidine or clonidine onthecharacteristics ofbupivacaine spinalblock. Acta AnaesthesiolScand2006; 50(2):222-7.

48. Jorm CM,StamfordJA. Actions of thehypnotic anaesthetic, dexmedetomidine,onnoradrenaline release and cellfiring inrat locus coeruleus slices. Br J Anaesth1993; 71:447-9.

49. RoudetC, MouchetP, Feuerstein C,Savasta M. Normal distribution of α_2-adrenoceptors inthe ratspinalcordandits modification after noradrenergic denervation:A quantitativeautoradiographicstudy. JNeurosciRes 1994; 39:319-29.

50. Stone LS,Broberger C, VulchanovaL, WilcoxGL, HokfeltT, Riedl MS,et al. Differentialdistribution of $\alpha_{2A}$and α_{2C} adrenergicreceptor immunoreactivityin the ratspinal cord.J Neurosci1998; 8:5928-37.

51. BromagePR, Burfoot MF, Crowell DE,PettigrewRT. Quality of epiduralblockade.Influenceofphysicalfactors.BrJ Anaesth 1964; 36:342-52.

52. RamsayMA, Savege TM, Simpson BR,Goodwin R.Controlledsedation withalphaxalone-alphadolone. BrMedJ1974; 2(5920):656-9.

53. .EjnarEriksson. Illustrated Handbook in localanesthesia.2nd Edition. Lloyd-luke(London UK):1979,13

54. A.R Aitkenhead, G. Smith. Text book of Anesthesia. 3rd Edition. Churchill livingstone(United States of America):1996, 435-444.

55. Goodman and Gilman. The pharmacological basis of therapeutics.11th Edition. McGraw Hill publishing division (United States of America):2006, 204-214.

56. Robert K Stoelting. Pharmacology and physiology in anesthesia practice. 3rd Edition. Lippincott–Raven publishers (United States of America):1999, 77-112.

57. SS Harsoor, D Devika Rani, Bhavana Yalamuru, K Sudheesh, S S Nethra. Effect of supplementation of flow dose intravenous dexmedetomidine on characteristics of spinal anaesthesia with hyperbaric bupivacaine. 77A2013.57 (3).265-269.

58. Maze M, Tranquilli W: Alpha-2 adrenoreceptor agonists: Defining the role in clinical anaesthesia. Anesthesiology 1991; 74:581-605.

59. Gerlach AT, Dasta JF: Dexmedetomidine: An updated review. Ann Pharmacother 2007;41:245-252.

60. Talke P, Richardson CA, Scheinin M, Fisher DM. Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. Anaesthesia Analgesia 1997; 85:1136-42

61. Paris A, Tonner PH. Dexmedetomidine in anaesthesia. Curr Opin Anaesthesiol 2005; 18: 412-8

62. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of

dexmedetomidine in humans. Anaesthesiology. 2000; 93:382-94

63. Talke P, Chen R, Thomas B, Aggarwall A, Gottlieb A, Thorborg P, Heard S, Cheung A, Son SL, Kallio A. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. Anaesthesia Analgesia 2000; 90:834-9
64. Gerlach AT, Dasta JF: Dexmedetomidine: An updated review. Ann Pharmacotherapy 2007; 41:245-252.
65. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of IV Dexmedetomidine in Humans II. Haemodynamic changes. Anaesthesiology 1992; 77:1125-33.
66. Villela NR, Nascimento junior P. Dexmedetomidine in Anaesthesiology. Rev Bras Anestesiol 2003 Feb; 53(1):97-l 13.
67. Kallio A, Scheinin M, Koulu M, Riitta Ponkilainen, Heikki Ruskoaho, Osmo Viinamaki, and Harry Scheinin. Effects of Dexmedetomidine, a selective α2 adrenergic agonist on haemodynamic control mechanism. Clinical pharmacology and therapeutics 1989; 46: 33-42.
68. Duke P, Maze M, Morrison P. Dexmedetomidine: a general overview. International Congress and Symposium Series (221). 1998(theme issue): 13.

69. De Wolf AM, Fragen RJ, Avram MJ, et al: The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. Anesth Analg 2001; 93:1205-1209.

70. Venn RM, Karol MD, Grounds RM: Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive caret. Br JAnaesth 2002; 88:669-675.

71. Ramsay MA, Luterman DL: Dexmedetomidine as a total intravenous anaesthetic agent. Anesthesiology 2004; 101:787-790.

72. Guo TZ, Jiang JY, Buttermann AE, Maze M: Dexmedetomidine injection into the locus coeruleus produces antinociception. Anesthesiology 1996; 84:873-881.

73. Venn RM, Bradshaw CJ, Spencer R, et al: Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 1999; 54:1136- 1142.

74. Venn RM, Hell J, Grounds RM: Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. Crit Care 2000; 4:302-308.

75. Nacif-Coelho C, Correa-Sales C, Chang LL, Maze M: Perturbation of ion channel conductance alters the hypnotic response to the alpha 2-adrenergic agonist dexmedetomidine

in the locus coeruleus of the rat. Anesthesiology 1994; 81:1527-1534.

76. Talke P, Tong C, Lee HW, et al: Effect of dexmedetomidine on lumbar cerebrospinal fluid pressure in humans. Anesth Analg 1997;85:358-364.
77. Ebert TJ, Hall JE, Barney JA, et al: The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000; 93:382-394.
78. Hogue Jr CW, Talke P, Stein PK, et al: Autonomic nervous system responses during sedative infusions of dexmedetomidine. Anesthesiology 2002; 97:592-598.
79. Riker RR, Fraser GL: Adverse events associated with sedatives, analgesics, and other drugs that provide patient comfort in the intensive care unit. Pharmacotherapy 2005; 25:8S-18S.
80. Aho M, Erkola O, Kallio A, et al: Dexmedetomidine infusion for maintenance of anaesthesia in patients undergoing abdominal hysterectomy. Anesth Analg 1992; 75:940-946.
81. Kanchan Gupta, Sunil Katyal, Sandeep Kaushal, Geeta Mittal, Randomised double-blind comparative study of dexmedetomidine and tramadol for post-spinal anaesthesia

shivering. Indian Journal of Anaesthesia, 2014, 58 (3) : 257-262.

82. Annamalai A, Singh S, Singh A, Mahrous DE, Can Intravenous Dexmedetomidine Prolong Bupivacaine Intrathecal Spinal Anaesthesia? 2013; J Anesth Clin Resm 4:372.
83. DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: A review of clinical applications. Curr Opin Anaesthesiol 2008;21:457-61
84. Yazbek-Karam VG, Aouad MA. Perioperative Uses of Dexmedetomidine. Middle East J Anesthesiol 2006;18:1043-58
85. Kim YS, Kim YI, Seo KH, Kang HR. Optimal dose of prophylactic dexmedetomidine for preventing postoperative shivering. Int J Med Sci. 2013;10:1327–1332.
86. Usta B, Gozdemir M, Demircioglu RI, Muslu B, Sert H, Yaldiz A. Study to evaluate the effect of dexmedetomidine on shivering during spinal anaesthesia. Clinics (Sao Paulo). 2011;66(7):1187-91.
87. Andrew C. Kontak, Ronald G. Victor, Wanpen Vongpatanasin, Dexmedetomidine as a Novel Countermeasure for Cocaine-Induced Central

Sympathoexcitation in Cocaine-Addicted Humans, Hypertension. 2013, 61: 388-394.

88. Alka Shah, Ila Patel, Rachana Gandhi, Haemodynamic effects of intrathecal dexmedetomidine added to ropivacaine intraoperatively and for postoperative analgesia.Int J Basic Clin Pharmacol. 2013; 2(1): 26-29.

89. Mahima Gupta, S. Shailaja, and K. Sudhir Hegde. Comparison of Intrathecal Dexmedetomidine with Buprenorphine as Adjuvant to Bupivacaine in Spinal Asnaesthesia. J Clin Diagn Res. 2014; 8(2): 114–117.

90. MS Saravana Babu, Anil Kumar Verma, Apurva Agarwal, Chitra MS Tyagi, Manoj Upadhyay, Shivshenkar Tripathi. A comparative study in the post-operative spine surgeries: Epidural ropivacaine with dexmedetomidine and ropivacaine with clonidine for post-operative analgesia. Indian Journal of Anaesthesia. 2013, 57(4): 371-376.

APPENDIX I

INSTITUTIONAL HUMAN ETHICS COMMITTEE CLEARANCE

Sree Mookambika Institute of Medical Sciences
Kulasekharam (K.K District, TN) 629161
Phone No: 04651-280866, Fax No. 04651-280740

Institutional Human Ethics Committee

Registered under CDSCO with Reg No. ECR/446/Inst/TN/2013

Ref. No. SMIMS/IHEC/2013/C/26 **Date: 27th December 2013**

Certificate

This is to certify that the Research Protocol Ref. No. **SMIMS/IHEC/2013/C/26,** entitled "A Study on The Anaesthetic and Analgesic Effects of Intravenous Dexmedetomidine as Premedication for Spinal Anaesthesia" submitted by Dr. Suzanne Prasad, Postgraduate of Department of Anaesthesiology, SMIMS has been approved by the Institutional Human Ethics Committee at its meeting held on 19th of December 2013.

[This Institutional Human Ethics Committee is organized and operates according to the requirements of ICH-GCP/GLP guidelines and requirements of the Amended Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945 of Government of India.]

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES * KULASEKHARAM * IHEC Date 27/12/2013

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
Professor of Pharmacology and HOD
SMIMS, Kulasekharam [K.K District]
Tamil Nadu -629161

APPENDIX II

CONSENT FORM

PART 1OF 2

INFORMATION FOR PARTICIPANTS OF THE STUDY

Dear volunteers,

We welcome you and thank you for your keen interest in volunteering for this research project. Before you become a part of the study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, purpose, benefits, risks, discomforts, precautions and the information about how this project will be carried out. It is important that you read and understand the contents of this form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are to ask the study personnel or contact the person mentioned below before you give your consent and also at any time during the entire course of the project you are free to retreat from the study.

Name of the Principal Investigator: Dr. Suzanne Prasad

Postgraduate – M.D Anaesthesiology

Sree Mookambika Institute of Medical Sciences,

Kulasekharam

Name of the Guide : **Dr. V.G. Jayaprakash, MD**

Professor

Department of Anaesthesiology

Sree Mookambika Institute of Medical Sciences

Kulasekharam, Kanyakumari District:

Tamil Nadu 629161

Name of the Co-Guide : **Dr. Rommy Geever T, MD**

Assistant Professor

Department of Anaesthesiology

Sree Mookambika Institute of Medical Sciences

Kulasekharam, Kanyakumari District:

Tamil Nadu 629161

Institution Details with Address: Sree Mookambika Institute of Medical Sciences,

Kulasekharam

Kanyakumari District – 629161

Tamil Nadu

Title of the study:

"A study on the anaesthetic and analgesic effects of intravenous dexmedetomidine as premedication for spinal anaesthesia."

Background information:

Spinal anaesthesia is a widely practiced anaesthetic technique for lower abdominal and lower limb surgeries. Dexmedetomidine is a highly selective α2 - adrenergic receptor agonist with a relatively high α2/α1 activity. The present study evaluates the use of intravenous dexmedetomidine as premedication in bupivacaine induced spinal anaesthesia.

Aims and Objectives:

Primary objective

The objective of our present study is to evaluate the effects of intravenous Dexmedetomidine as premedication on the onset, level and duration of sensory and motor blockade, analgesia and sedation in patients posted for infraumbilical surgeries under Bupivacaine (hyperbaric, 0.5%, 3mL) spinal anaesthesia.

Secondary objectives

- The level of sedation achieved in comparison with control group.
- To evaluate the post-operative analgesia requirements relative to control group.
- To evaluate perioperative hemodynamic stability in the study group.

- To assess possible complications.

Scientific justification of the study:

Neuraxial block for lower abdominal surgeries are becoming widely popular owing to its many advantages over general anaesthesia. Spinal anaesthesia consists of transient interruption of nerve transmission by injecting a local anaesthetic (Bupivacaine 15mg) solution in the subarachnoid space. The role of an anaesthesiologist is to render pain free surgical procedures.

Anxiety is the most prevalent presentation in patients in the perioperative period starting from few days prior to surgery and reaches its peak just before induction of anaesthesia. Anxiety is also an intraoperative problem in patients undergoing surgical procedures under regional anaesthesia which may be the reason for various manifestations like increase in oxygen consumption, respiratory rate and heart rate due to circulating level of intrinsic catecholamines and their untoward effects. Control of anxiety and pain is a challenge to any anaesthesiologists in an attempt to control the metabolic derangements and for the safety and comfort of the patient.

Dexmedetomidine is an eminent, potent α_2-adrenoceptor agonist that acts centrally. It has the ability to sedate, hypnotize and provide analgesia, thereby extending the duration of sensory and motor block acquired with intrathecal block while still preserving patient arousability and ventilatory

function. It can be used as premedication, during induction of anaesthesia intravenously and as an adjuvant for intrathecal block with Bupivacaine.

This dissertation is a study on the effects of i.v Dexmedetomidine 0.5mcg/kg as premedication for analgesia, sedation and prolongation of spinal anaesthesia in patients posted for surgeries under subarachnoid block with hyperbaric Bupivacaine 0.5% (3ml or 15mg).

Procedure of the study:

Spinal anaesthesia has different steps. Patient will first be preloaded with 500mL of RL through 18G cannula, premedication includes Inj. Ranitidine 50mg i.v, Inj. Metoclopramide 10mg slow i.v and Group I will be given Dexmedetomidine 0.5mcg/kg (over 10mins) and Group II – 10mL of normal saline, half an hour before the surgery. The Multiparameter monitors will be attached and the heart rate, blood pressure and oxygen saturation will be constantly recorded from the time of administration of premedication and continued postoperatively. 15mg of Hyperbaric, 0.5% heavy Bupivacaine will be administered intrathecally into L_3-L_4 after proper positioning of the patient and the sensory and motor block, sedation score and postoperative analgesia will be assessed throughout for the study purpose.

1. Expected risk of the participants:

   Tachy/bradycardia and/or hyper/hypotension

2. Expected benefits of the patients:

   There may not be any personal benefits, but this study will be beneficial for the betterment of the health science.

3. Maintenance of Confidentiality:

   All data collected for the study will be kept confidentially and would reflect on general statistical evaluation only and would not reveal any personal details.

4. Why have you been chosen to be in the study?

   You are undergoing spinal anaesthesia and fulfil the criteria of selection.

5. How many people will be in the study? 60
6. Agreement of compensation to the patient: No
7. Anticipated prorated payment, if any, to the participant(s) of the study: Nil
8. Can I retreat from the study at any time during the study period? Yes
9. If there are any new findings / information, would I be informed? : Yes
10. Expected duration of Participant's participation in the study: Throughout the day of surgery
11. Any other pertinent information: No

12. Whom do I contact for further information? : Dr. Suzanne Prasad

For any study related queries, you are free to contact

Dr. Suzanne Prasad

M.D Postgraduate student

Department of Anaesthesiology

Sree Mookambika Institute of Medical Sciences,

Kulasekharam

Mobile number: +918098890801

e-Mail I.D: suzanne_szn07@yahoo.co.uk

Place:

Date:

Signature of the Principal Investigator

Signature of the Participant

CONSENT FORM

PART 1 OF 2

PARTICIPANTS' CONSENT FORM

The principal investigator has explained to me the details of the research "a study on the anaesthetic and analgesic effects of intravenous dexmedetomidine as premedication for spinal anaesthesia" to be conducted in the Department of Anaesthesiology, Sree Mookambika Institute of Medical Sciences, Kulasekharam. She has explained to me that by being a part of this study no new medication will be tried on me. I am aware of my right to opt out of this study at any stage without any hindrance to my ongoing treatment. No additional financial burden will be placed on me by being part of this study. Data collected for the study will be kept under strict confidentiality and would not reveal any personal details. The principal investigator has also explained in detail the procedure of administering the drug before spinal anaesthesia and the possible adverse effects associated with its use. Keeping the above facts in mind I, whole heartedly, without any compulsion agree to participate in this study.

Signature of the patient: Signature of the investigator:

Address of the patient: Address of the investigator:

Signature of the witness:

Address of the witness:

APPENDIX III

PROFORMA FOR ANAESTHESIA RECORD

Pre-Anaesthetic Evaluation

Date:

Name of the patient: Age/Sex:

Address: I.P No:

History From:

Surgical Diagnosis:

Proposed Surgery:

Previous Anaesthesia:

Relevant Past History:

Current Medications (if any):

Known Allergies:

General Physical Examination:

(Good/Fair/Sick/Conscious/Drowsy/Unconscious)

Pulse rate: Blood Pressure: Temperature:

Pallor: Cyanosis: Oedema:

Height (cms): Weight (kgs):

Airway Assessment: M.P ☐ T-M distance: ☐

M-O distance: ☐ Neck Movements: full/limited/none

Teeth: (poor/loose) Micrognathia: ☐

Short muscular neck: ☐ Morbid Obesity: ☐ Others:

Systemic Examination Findings:

Pulmonary Examination: (smoker/not)

Cardiovascular Examination:

Abdominal Examination: (alcoholic/not)

Neuro-muscular Examination:

INVESTIGATIONS AND LABORATORY REPORTS

Haemoglobin:

TC:

DC:

ESR:

Blood Sugar: Fasting:

Post-prandial:

Random:

LFT:

Serum Bilirubin:

Direct Bilirubin:

Indirect Bilirubin:

SGOT:

SGPT:

SAP:

Blood Urea:

Serum Creatinine:

Blood Group and Rh factor:

Urine Routine:

Serology:

ECG:

X-ray Chest:

ECHO/TMT/Others:

S. Protein:

Total Protein:

Albumin Globulin ratio:

BT:

CT:

Others:

ASA Physical Status: 1 2 3 4 5 6 E

Patient accepted for Anaesthesia: Yes/No

Plan of Anaesthesia:

Pre-medications and Instructions:

Name of the Anaesthesiologist: **Signature**

APPENDIX IV

Anaesthesia Record

Date:

Name of the Patient:

Age/Sex:

I.P No:

Anaesthesiologist:

Surgeon:

Procedure: **Position:**

Pre-procedure assessment:

Consent signed: ☐ Chart Reviewed: ☐

NPO since: Full stomach: ☐

Patient reassessed prior to anaesthesia: ☐

Pre-anaesthetic state:

(Awake/calm/anxious/uncooperative/sedated/unconscious)

Baseline vitals: Pulse rate: Blood Pressure:

Respiratory rate: Temperature:

SpO_2:

Monitors and Equipment:

Non-invasive B.P: ☐ Continuous ECG: ☐ Pulse ☐

Oximeter:

Anaesthetic Technique:

Position of the patient: Needle Type and size:

Site:

Drug: Dose:

IV Fluids:

Intraoperative Medications:

Urine output:

Intraoperative Vitals monitoring:

Time	HR	MAP	SPO2
5 mins			
15mins			
30 mins			
45 mins			
60 mins			
1h 15 mins			
1h 30 mins			
1h 45 mins			
2 h			
2 h 15 mins			
2 h 30 mins			
2 h 45 mins			
3 h			

TIME	SENSORY	MOTOR
0		
10		
20		
30		
40		
50		
60		
70		
80		
90		
100		
110		
120		
130		
140		
150		
160		
170		
180		
190		
200		
210		
220		
230		
240		
260		
280		
300		
320		

The highest sensory block level achieved:

Recovery time for sensory blockade (two - dermatome regression):

Recovery time for motor blockade to Bromage 2:

Time to first request for analgesia:

The Ramsay sedation score at

10 mins	
30 mins	
50 mins	
70 mins	
90 mins	
110mins	
120 mins	

Postoperative status of the patient:

B.P: Pulse rate: Temperature:

SpO_2:

Postoperative instructions:

Signature of the Anaesthesiologist

Serial No.	Age	Sex	Height	Weight	ASA Grade	Observation at regular intervals (Time in minutes) in GROUP C																								
						Baseline					5					15					30					45						
						HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)
1	32	M	160	69	2	68	130	96	107	99	66	128	86	100	100	67	126	72	90	99	68	120	72	88	99	66	118	68	85	98	65	116
2	34	F	154	67	1	76	124	84	97	98	77	98	66	77	99	78	104	58	73	98	75	94	60	71	99	74	110	62	78	98	73	88
3	22	M	159	65	2	58	92	64	73	98	56	96	50	65	99	45	100	56	71	99	54	104	56	72	99	55	102	54	70	99	58	106
4	38	F	161	68	2	72	120	74	89	99	70	94	60	71	98	71	98	64	64	98	73	92	60	71	100	74	98	68	78	98	77	100
5	42	F	157	71	1	87	130	90	103	98	85	91	61	71	99	83	100	65	77	97	85	100	60	73	99	86	100	59	73	99	85	104
6	46	F	162	70	2	77	110	66	81	97	78	94	56	69	98	75	94	56	69	99	76	90	52	65	98	75	92	50	64	98	78	94
7	26	M	167	68	1	84	130	90	103	100	86	120	76	91	99	85	120	74	89	100	83	110	70	83	98	83	98	76	83	99	83	96
8	48	M	153	62	1	65	124	74	91	100	68	120	62	81	99	67	110	56	74	100	64	100	50	67	99	65	98	58	71	99	62	100
9	52	M	158	66	1	58	130	80	97	97	52	96	60	72	98	48	90	52	65	97	51	98	56	70	100	55	100	62	75	100	54	100
10	46	M	164	60	2	67	110	68	82	98	65	106	58	74	98	64	104	54	71	98	66	102	52	69	98	63	98	50	66	100	62	102
11	52	F	148	72	1	73	124	78	93	98	75	91	61	71	97	73	100	65	77	98	73	100	60	73	99	75	100	59	73	99	73	104
12	34	M	159	68	2	89	130	86	88	97	88	114	68	83	98	85	110	60	77	99	84	96	62	73	99	86	104	64	77	98	85	90
13	38	M	164	66	2	54	124	82	96	97	53	90	70	77	99	57	96	80	85	100	54	100	70	80	100	56	98	72	81	97	54	100
14	40	M	169	62	1	85	130	94	106	99	87	120	74	89	98	86	120	80	93	99	88	120	80	93	99	85	110	70	83	98	83	110
15	42	F	172	63	2	79	110	76	87	99	77	90	56	67	99	74	96	60	72	99	78	100	72	81	98	73	100	60	73	99	72	110
16	38	M	168	69	2	84	120	80	93	99	83	110	70	83	98	82	90	46	61	97	83	96	46	63	98	84	96	56	69	98	85	96
17	36	F	156	66	1	68	120	80	93	98	68	110	68	82	97	56	110	60	77	98	59	110	60	77	99	58	90	52	65	99	64	100
18	40	M	154	68	2	87	124	84	97	100	85	92	52	65	98	86	124	82	96	98	86	124	66	85	99	85	130	74	93	100	87	120
19	26	M	162	70	1	92	124	62	83	99	93	96	60	71	99	92	94	62	73	99	94	92	58	69	100	92	98	54	69	97	93	94
20	28	M	158	72	2	84	120	76	91	98	86	130	78	95	100	84	120	76	91	97	86	134	88	103	100	85	120	80	93	100	83	104
21	24	M	166	67	2	78	110	70	83	99	76	102	72	82	100	76	104	72	83	99	71	120	80	93	99	72	110	76	87	99	71	110
22	38	F	163	69	1	75	140	90	107	97	74	140	90	107	100	73	120	70	87	100	76	120	70	87	99	75	110	70	83	98	77	96
23	48	F	155	61	1	62	124	88	100	98	61	90	60	70	100	62	100	64	76	100	63	100	60	73	98	61	98	59	72	97	63	100
24	56	M	174	59	1	85	120	72	88	99	82	96	62	73	98	83	88	46	60	99	84	96	60	72	98	83	96	56	69	98	85	98
25	44	M	175	68	2	96	130	90	103	100	91	134	88	103	99	92	120	73	89	98	92	130	76	94	98	93	110	63	79	99	95	96
26	54	M	166	63	2	75	110	70	83	97	76	110	70	83	98	78	120	76	91	97	77	110	70	83	98	75	120	80	93	100	76	120
27	28	M	167	74	2	68	120	80	93	98	65	120	80	93	98	65	120	80	93	98	64	124	84	97	97	67	110	80	90	99	65	110
28	32	M	170	76	2	76	124	82	96	99	77	90	50	63	97	74	120	80	93	99	76	110	70	100	97	77	110	70	83	98	73	110
29	34	M	169	70	1	92	130	90	103	98	90	140	100	113	99	90	120	80	93	99	89	120	70	87	99	84	110	80	90	97	86	120
30	36	M	168	68	1	86	110	72	85	98	82	112	74	87	97	81	116	76	89	98	88	114	78	90	98	86	116	72	87	99	85	118

								Observation at regular intervals (Time in minutes) in GROU																		
60			75					90					105					120					135						
DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)
64	81	98	64	118	66	83	98	66	118	62	81	100	64	114	60	78	97	67	114	58	77	99	68	118	64	82	98	65	118
56	67	99	70	98	65	76	98	71	110	70	83	99	70	110	74	86	98	70	112	68	83	98	72	120	80	93	97	73	110
58	74	99	58	106	56	73	100	54	104	56	72	100	55	86	50	62	99	56	104	52	69	98	56	108	58	75	99	58	106
70	80	98	75	110	68	82	99	76	110	70	83	100	79	112	80	91	99	76	120	76	91	99	77	130	78	95	97	76	124
60	75	98	84	99	63	75	98	84	97	61	73	99	87	104	69	81	100	86	120	80	93	99	85	120	80	93	98	86	120
56	69	98	76	92	56	68	99	74	90	54	66	98	77	88	46	60	99	75	90	52	65	99	76	90	52	65	98	78	92
72	80	99	88	110	74	86	98	86	120	74	89	99	84	120	76	91	99	86	114	72	86	98	85	130	70	90	100	88	120
60	73	98	61	100	60	73	97	63	94	56	69	98	65	100	66	77	98	64	110	74	86	97	63	120	76	91	99	64	120
60	73	99	54	110	70	83	97	56	112	70	84	99	54	120	80	93	97	56	120	80	93	97	60	124	78	93	98	66	124
54	70	98	63	94	52	66	98	62	98	54	69	98	63	102	58	73	97	64	108	58	75	98	62	106	52	70	98	66	104
60	75	98	75	99	63	75	99	75	97	61	73	99	73	104	69	81	99	75	120	80	93	99	74	120	80	93	99	75	120
58	69	100	81	110	76	87	99	82	110	72	85	99	84	124	76	92	98	86	110	70	83	98	82	120	80	93	100	83	120
70	80	97	52	92	68	76	98	51	100	70	80	98	53	100	68	79	100	52	100	66	77	98	55	110	70	83	100	58	110
60	77	97	88	112	60	77	97	84	100	60	73	98	85	120	80	93	99	88	120	80	93	97	86	130	86	101	99	89	130
70	83	100	74	110	68	82	99	79	110	70	83	99	78	104	64	77	98	76	136	96	109	99	77	140	92	108	98	75	130
52	67	98	83	106	64	78	97	85	110	70	83	99	83	110	70	83	98	83	120	70	87	100	86	120	80	93	98	84	120
60	73	99	51	100	60	73	98	52	100	60	73	99	54	100	70	80	97	55	110	70	83	100	56	120	80	93	99	58	120
72	88	100	88	114	62	79	100	85	120	70	87	100	86	128	78	95	100	85	120	80	93	99	84	120	80	93	100	86	134
56	69	98	91	94	58	70	100	92	92	56	68	99	92	98	52	67	98	93	94	56	69	98	92	104	58	73	99	91	106
64	77	99	85	100	60	73	98	82	98	60	73	98	81	104	70	81	99	82	110	70	83	97	83	120	80	93	98	82	124
70	83	100	69	110	68	82	97	70	110	70	83	97	72	104	64	77	98	70	136	96	109	98	68	140	92	108	97	74	130
72	80	99	74	92	68	76	97	73	96	74	81	100	74	110	70	83	99	77	120	74	89	99	74	110	70	83	99	75	120
60	73	99	64	98	58	71	98	63	96	60	72	99	66	100	70	80	98	64	110	68	82	100	63	124	76	92	97	62	124
60	73	98	84	94	52	66	99	82	90	48	62	98	81	92	48	63	97	85	90	46	61	98	86	94	48	63	98	84	96
60	72	98	94	98	58	71	99	92	100	60	73	98	93	100	60	73	100	92	110	76	87	98	94	120	88	99	99	91	124
80	93	99	75	110	70	83	99	76	130	90	103	97	77	130	90	103	100	74	130	80	97	100	77	120	80	93	99	76	120
70	83	97	66	110	70	83	99	68	110	60	77	98	64	120	80	93	99	66	120	80	93	97	62	130	80	97	98	65	130
70	83	97	78	134	74	94	98	79	110	70	83	99	75	120	74	89	97	74	120	80	93	99	77	114	78	90	98	79	130
80	93	99	90	130	100	110	98	84	130	80	97	100	85	140	90	107	98	82	140	90	107	98	80	120	80	99	100	82	120
74	89	98	83	116	76	89	99	84	118	72	87	100	82	110	74	86	99	87	114	76	89	100	84	118	72	87	99	88	112

UP C																			
150			165					180							Sensory block				
																Recovery time (mins)			
DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	Use of Atropine	Use of Ephedrine	Highest block level	Sensory block	Motor block	First analgesia (mins)	Maximum sedation scorre
64	82	99	67	120	68	85	98	69	118	66	83	99	N	N	T6	70	110	110	2
68	82	98	72	124	78	93	99	71	130	86	101	98	N	N	T8	70	120	130	2
54	71	99	60	108	54	72	97	61	106	54	71	98	Y	N	76	70	110	120	2
70	88	98	75	130	80	97	97	77	130	80	97	99	N	N	T5	70	140	160	2
90	100	98	86	120	80	93	99	84	130	90	103	97	N	N	T6	80	130	150	2
54	67	98	74	94	56	69	98	75	96	56	69	100	N	Y	T8	80	150	190	2
80	93	99	87	130	86	101	99	85	134	86	102	98	N	N	T7	70	110	130	2
80	93	98	62	130	76	94	100	65	132	84	100	98	N	N	T5	70	130	160	2
82	96	98	64	130	90	103	100	56	134	92	106	99	Y	N	T6	80	110	120	2
56	72	99	63	106	54	71	99	62	108	56	73	98	N	Y	T5	70	120	150	2
90	100	100	76	120	80	93	99	78	130	90	103	97	N	N	T7	80	150	170	2
70	87	100	85	130	80	97	98	84	134	88	103	99	N	N	T8	80	120	120	2
78	89	99	56	110	80	90	98	61	120	90	100	97	Y	N	T6	70	160	180	2
90	103	98	87	130	90	103	97	90	130	90	103	98	N	N	T6	70	170	190	2
90	103	98	76	130	96	107	97	76	134	88	103	99	N	N	T7	80	140	160	2
80	93	99	84	130	80	97	99	86	120	80	93	98	N	N	T5	80	170	180	2
80	93	98	60	130	80	97	98	61	130	80	97	100	Y	N	T7	90	150	170	2
94	107	97	83	120	80	93	99	85	130	90	103	100	N	N	T7	70	130	150	2
60	75	98	94	108	62	77	98	92	102	54	70	99	N	Y	T8	70	150	170	2
84	97	99	83	120	80	93	98	84	130	88	103	98	N	N	T6	70	110	130	2
90	103	100	78	130	96	107	99	75	134	90	103	99	N	N	T8	70	120	140	2
80	93	98	76	130	90	103	100	79	130	90	103	98	N	N	T6	90	140	160	2
76	92	98	66	120	80	93	100	62	120	80	93	98	N	N	T5	90	180	190	2
48	64	98	85	98	50	66	100	81	96	52	67	97	N	Y	T5	70	120	130	2
86	99	99	92	110	88	95	100	93	124	90	101	98	N	N	T6	80	130	140	2
80	93	99	78	110	80	90	100	74	110	70	83	99	N	N	T7	80	170	190	2
90	103	99	63	132	82	99	100	62	120	80	93	100	N	N	T7	80	160	170	2
90	103	98	77	124	76	92	100	78	124	88	100	98	N	N	T5	70	180	210	2
80	93	98	86	134	84	101	99	82	140	90	107	99	N	N	T6	90	130	150	2
74	87	99	81	116	74	88	98	86	112	78	89	99	N	N	T6	70	120	130	2

Serial No.	Age	Sex	Height	Weight	ASA Grade	Observation at regular intervals (Time in minutes) in GROUP D																																	
						Baseline					5					15					30					45					60					75					
						HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)
1	32	M	154	64	1	62	138	94	109	99	66	132	90	104	99	65	130	88	102	98	66	128	86	100	98	66	126	84	98	98	64	116	84	95	97	64	112	76	88	100	62
2	43	M	157	68	2	77	120	74	89	98	75	108	60	76	98	76	104	58	73	99	76	98	56	70	97	74	94	48	63	98	75	92	44	60	100	75	90	44	59	98	76
3	26	F	162	57	2	84	134	86	102	100	78	132	86	101	98	77	128	72	91	100	77	122	70	87	99	75	118	68	85	97	76	110	68	82	99	77	114	70	85	99	77
4	24	M	158	59	1	65	126	72	90	97	65	124	70	88	99	64	118	70	86	98	64	112	68	83	98	66	110	64	79	99	65	108	64	79	98	64	104	64	77	100	66
5	35	M	153	63	1	89	132	80	97	97	85	128	70	89	100	86	124	68	87	99	84	120	66	84	99	85	114	66	82	97	85	110	68	82	99	86	108	70	83	99	86
6	56	M	152	58	1	96	142	92	109	99	89	134	86	102	100	87	130	82	98	97	87	128	76	93	100	87	126	74	91	98	88	124	72	89	100	86	126	74	91	98	86
7	52	F	162	54	1	84	138	86	103	100	82	134	76	95	97	80	132	78	96	97	81	130	76	94	100	83	126	60	82	99	82	124	62	83	98	82	118	62	81	97	81
8	42	M	149	67	2	68	130	78	95	100	64	126	60	82	98	64	120	60	80	98	63	118	58	78	98	62	114	58	77	98	58	112	60	77	97	56	106	58	74	99	50
9	46	M	154	59	2	72	122	68	86	100	70	118	68	85	99	68	114	66	82	98	64	108	56	73	99	54	106	54	71	99	57	100	56	71	100	58	102	56	71	100	69
10	34	F	168	61	2	78	140	92	108	99	77	138	76	97	98	78	134	74	94	99	77	130	72	91	99	78	128	70	89	100	77	126	68	87	98	79	122	68	86	98	78
11	24	M	162	67	1	69	126	70	89	97	69	120	62	81	100	68	116	64	81	99	64	114	66	82	97	62	110	64	79	97	58	110	66	81	100	64	110	68	82	98	64
12	43	M	164	62	1	74	136	82	100	98	74	132	78	96	97	73	128	70	89	100	74	124	64	84	97	75	120	66	84	97	75	126	68	87	100	74	124	62	83	99	76
13	48	M	163	56	2	73	128	74	92	98	72	124	74	91	97	74	120	72	88	100	73	122	68	86	99	72	118	68	85	98	70	120	66	84	98	72	120	70	87	97	73
14	30	F	155	68	1	75	134	78	97	97	74	130	76	94	98	75	128	74	92	99	74	126	72	90	100	73	124	68	87	98	71	122	70	87	97	74	120	66	84	100	72
15	46	M	166	64	2	88	130	70	90	98	85	126	72	90	100	86	122	70	87	97	87	120	70	87	97	88	116	66	83	99	86	118	66	83	98	86	116	68	84	100	85
16	54	M	168	67	2	62	142	86	105	98	60	140	82	101	97	58	138	74	95	97	52	134	78	97	98	50	132	76	95	99	48	130	78	95	100	56	128	70	89	99	58
17	52	M	152	53	1	79	128	72	91	99	78	122	72	89	100	77	118	70	86	98	76	114	70	85	99	76	118	68	85	100	75	114	70	85	98	74	118	68	85	97	77
18	29	F	157	49	1	82	126	70	89	100	80	120	74	89	98	82	116	72	87	98	81	112	72	85	97	80	116	66	83	97	82	112	68	83	97	83	116	70	85	98	81
19	53	M	156	65	2	96	130	78	95	100	96	126	72	90	98	95	124	70	88	98	95	118	70	86	99	96	116	68	84	99	94	114	68	83	98	96	116	70	85	97	96
20	56	F	164	62	2	78	134	84	101	100	76	130	76	94	97	77	128	64	85	100	74	120	68	85	99	76	116	66	83	97	75	112	64	80	100	76	110	68	82	97	75
21	45	M	159	58	1	82	140	88	105	97	80	136	78	97	100	81	132	78	96	100	81	130	76	94	98	82	132	80	97	98	80	132	66	88	99	82	128	68	88	98	81
22	52	M	161	68	1	87	136	74	95	98	86	134	86	102	97	85	134	84	101	97	87	130	82	98	98	85	130	84	99	100	84	128	74	92	98	84	126	70	89	99	86
23	24	M	169	64	2	77	120	70	87	99	76	86	44	58	98	77	90	58	69	98	75	94	52	66	97	74	92	50	64	97	75	90	56	67	97	75	92	52	65	100	76
24	36	F	157	58	2	80	138	90	106	97	75	134	86	102	100	78	132	74	93	99	76	134	76	95	100	77	128	72	91	98	78	128	70	89	100	76	124	72	89	99	74
25	26	M	167	62	2	78	132	80	97	100	77	128	76	93	98	76	126	74	91	99	74	126	72	90	99	75	124	72	89	97	76	120	74	89	99	74	122	74	90	98	75
26	43	F	157	49	1	64	126	72	90	97	62	122	68	86	100	62	118	64	82	100	60	118	62	81	99	61	112	62	79	97	61	112	60	77	97	54	108	60	76	99	63
27	50	F	166	53	2	83	136	84	101	97	82	132	78	96	100	80	130	78	95	97	78	130	74	93	98	82	128	72	91	99	77	126	74	91	98	82	120	68	85	100	80
28	33	M	161	60	1	79	130	82	98	98	77	126	72	90	99	74	124	72	89	98	75	120	68	85	98	73	122	68	86	99	72	126	72	90	100	74	124	70	88	97	73
29	37	F	157	55	2	68	138	80	99	99	62	134	86	102	99	60	134	82	99	98	56	132	80	97	97	50	130	84	99	100	50	132	84	100	99	48	130	82	98	98	56
30	27	M	158	48	1	92	130	76	94	98	90	128	74	92	99	91	124	72	89	99	90	120	70	87	99	89	118	64	82	99	88	116	64	81	98	87	114	62	79	99	86

Observation at regular intervals (Time in minutes) in GROUP D																																		Use of Atropine	Use of Ephedrine	Sensory block			First analgesia (mins)	Maximum sedation scorre
90				105					120					135					150					165					180							Highest block level	Recovery time (mins)			
SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	SPO2 (%)				Sensory block	Motor block		
118	78	91	99	64	120	74	89	98	63	118	78	91	97	62	114	76	89	100	63	116	74	88	99	63	114	76	89	99	64	118	72	87	98	N	N	T7	110	180	220	3
92	48	63	97	75	90	46	61	97	75	90	48	62	98	76	94	50	65	99	74	96	52	67	99	75	94	56	69	99	75	92	58	69	99	N	Y	T5	160	180	240	3
110	68	82	98	75	112	68	83	99	76	112	64	80	99	77	110	64	79	98	77	110	62	78	98	75	112	68	83	98	76	112	70	84	98	N	N	T6	130	170	170	2
104	70	81	99	64	108	68	81	100	66	110	66	81	99	65	108	68	81	99	65	108	66	80	97	64	106	68	81	99	65	106	66	79	97	N	N	T8	160	180	300	3
106	68	81	99	85	108	70	83	99	84	106	70	82	98	88	110	68	82	100	85	108	68	81	97	86	110	66	81	100	87	108	64	79	100	N	N	T6	150	190	210	3
126	74	91	97	87	128	72	91	100	86	120	68	85	97	87	118	70	86	100	86	118	68	85	99	88	120	68	85	98	86	118	68	85	99	N	N	T7	120	170	220	2
120	68	85	97	80	118	56	77	98	81	116	56	76	99	82	114	60	78	99	83	114	62	79	98	82	116	64	81	97	83	114	64	81	98	N	N	T5	140	160	230	3
108	56	73	99	56	106	54	71	99	56	104	56	72	99	55	102	58	73	99	54	100	56	71	99	54	98	54	69	99	54	100	56	71	99	Y	Y	T7	160	180	310	3
98	52	67	100	68	94	52	66	99	68	102	54	70	100	66	102	54	70	98	66	100	56	71	97	66	98	56	70	100	69	100	54	69	98	Y	Y	T8	110	170	270	3
120	66	84	98	78	120	64	83	98	78	118	68	85	100	79	116	68	84	97	77	114	64	81	99	78	116	64	81	100	76	118	66	83	99	N	N	T6	150	160	250	3
106	66	79	99	63	108	68	81	100	65	108	58	75	100	66	112	66	81	97	63	118	64	82	99	64	120	68	85	99	68	122	70	87	98	Y	N	T8	160	180	230	3
126	66	86	98	76	118	68	85	100	74	116	62	80	100	74	116	66	83	99	74	116	64	81	98	75	118	68	85	98	74	114	66	82	99	N	N	T6	190	200	190	3
116	68	84	100	74	114	64	81	97	71	114	66	83	99	73	118	68	85	98	73	120	70	87	97	72	118	64	82	97	71	116	62	80	100	N	N	T7	150	190	200	3
124	68	87	97	73	124	68	87	98	72	126	70	89	99	74	126	68	87	100	75	120	64	83	100	70	118	66	83	100	70	118	68	85	99	N	N	T8	130	180	270	3
112	66	81	100	86	110	68	82	100	84	108	60	76	98	88	106	60	75	99	87	104	60	75	100	86	100	58	72	99	86	108	56	73	98	N	N	T6	120	180	260	3
126	68	87	100	58	122	70	87	98	58	124	68	87	99	57	122	64	83	100	57	118	68	85	99	57	122	70	87	98	55	118	70	86	99	Y	N	T5	170	200	210	3
114	68	83	100	76	112	68	83	99	76	110	68	82	98	74	110	68	82	98	77	108	68	81	98	75	106	68	81	98	76	110	68	82	100	N	N	T7	130	190	250	3
116	70	85	100	81	114	70	85	98	82	108	66	80	100	83	108	64	79	100	81	106	66	79	97	80	110	70	83	98	80	112	70	84	99	N	N	T6	160	190	270	3
118	70	86	98	95	120	72	88	100	94	116	68	84	99	96	118	72	87	97	94	120	72	91	97	95	116	66	83	99	96	118	68	85	98	N	N	T6	130	180	310	3
106	60	75	99	74	102	62	75	98	76	102	64	77	99	74	104	62	76	98	75	106	62	77	98	76	106	64	78	100	77	104	66	79	99	N	N	T7	120	170	260	2
126	70	89	97	80	128	68	88	97	82	126	72	90	98	81	128	70	89	98	78	124	68	87	99	78	122	64	83	97	79	122	68	86	97	N	N	T5	110	170	210	3
126	72	90	98	86	124	70	88	99	85	122	70	87	98	85	120	68	85	99	86	116	64	81	100	85	120	68	85	99	85	118	64	82	97	N	N	T6	110	160	280	3
90	54	66	99	74	92	56	68	98	75	94	52	66	98	73	90	56	67	99	74	92	54	67	99	75	90	48	62	98	73	92	52	65	99	N	Y	T5	150	190	270	3
122	70	87	98	76	120	68	85	99	77	118	68	85	98	78	118	68	85	98	78	120	72	88	100	76	118	64	82	100	76	118	70	86	98	N	N	T7	110	170	260	3
120	70	87	99	75	118	68	85	97	76	116	68	84	97	74	118	64	82	97	75	116	64	81	99	73	112	62	79	98	73	110	60	77	98	N	N	T6	120	190	210	2
106	62	77	100	62	108	64	79	100	61	104	58	73	99	63	102	62	75	98	61	104	62	76	99	60	102	64	77	99	61	100	60	73	100	Y	N	T7	140	180	220	3
116	64	81	99	81	114	62	79	99	80	118	70	86	99	76	120	72	88	100	75	120	70	87	98	80	118	68	85	97	78	114	68	83	99	N	N	T8	150	180	250	3
118	68	85	100	77	118	68	85	98	75	114	62	79	97	73	118	64	82	99	75	116	70	85	98	73	116	82	93	99	74	114	64	81	98	N	N	T6	150	190	210	3
128	78	95	99	58	126	74	91	99	62	126	74	91	99	64	124	76	92	99	63	120	74	89	99	61	122	76	91	98	60	124	72	89	98	Y	N	T5	120	170	240	3
110	62	78	99	87	108	60	76	99	86	110	62	78	99	85	110	64	79	98	84	112	62	79	100	82	112	64	80	97	81	114	64	81	99	N	N	T6	140	180	230	3